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(54) Title: SUBSTITUTED PYRROLIDIN-3-YL-ALKYL-PIPERIDINES USEFUL AS TACHYKININ ANTAGONISTS		
(57) Abstract The present invention relates to substituted pyrrolidinyl-3-yl-alkyl-piperidines, their stereoisomers, and pharmaceutically acceptable salts thereof and processes for preparation of the same. The compounds of the present invention are useful in their pharmacological activities such as tachykinin antagonism, especially substance P and neurokinin A antagonism, and the like. Compounds having the property of tachykinin antagonism are indicated for conditions associated with neurogenic inflammation and other diseases described herein.		

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SUBSTITUTED PYRROLIDIN-3-YL-ALKYL-PIPERIDINES USEFUL AS TACHYKININ
ANTAGONISTS

10 This is a continuation-in-part of Serial No. 08/058,606
filed May 6, 1993, which is herein incorporated by
reference. Divisional application Serial No. 08/218,413,
filed March 28, 1994 is also incorporated by reference.

15 The present invention relates to substituted
pyrrolidin-3-yl-alkyl-piperidines, isomers, and
pharmaceutically acceptable salts thereof (herein also
referred to as compounds or compounds of formula (1)) and
processes for preparation of the same. It is an object of
20 the present invention, therefore, to provide new and useful
compounds and pharmaceutically acceptable salts thereof,
and processes for their preparation.

 The compounds of the present invention are useful in
25 their pharmacological activities such as tachykinin
antagonism, especially substance P and neurokinin A
antagonism, and the like. Antagonism of tachykinin
responses can be elicited through blocking of tachykinin
receptors. Three general classes of tachykinin receptors
30 have been defined by their binding preference to substance
P (neurokinin 1 receptors (NK₁)), neurokinin A (neurokinin 2
receptors (NK₂)), and neurokinin B (neurokinin 3 receptors
(NK₃)). One object of the present invention is to provide
new and useful antagonists of tachykinins, especially
35 substance P and neurokinin A (NKA). Similarly, antagonism
of neurokinin B (NKB) activities may be important. A
particular object of the present invention are those
compounds that exhibit both NK₁ and NK₂ receptor antagonism.

Compounds having the property of tachykinin antagonism are indicated for conditions associated with neurogenic inflammation. Neuropeptides, including the tachykinins substance P and neurokinin A, are released from capsaicin-sensitive sensory C-fiber neurons. These peptides produce local effects which may be tissue specific including vasodilation, microvascular leakage, mucus secretion, inflammatory cell recruitment and priming, smooth muscle contraction and neuronal modulation. Generally, antagonism of the effects of substance P on its preferred receptor, i.e. NK₁, will not prevent the effects of NKA on its preferred receptor, i.e. NK₂. Therefore, the potential benefits of having an antagonist at both NK₁ and NK₂ receptors would be to reduce or prevent clinical manifestations of a disease which are mediated through both receptors.

A further object of the present invention is to provide compounds, or pharmaceutically acceptable salts thereof, for the treatment and prevention of various diseases in a patient in need thereof. Because the compounds of the present invention are tachykinin antagonists, they are potentially useful in the treatment of conditions associated with neurogenic inflammation, including asthma, allergies, bronchitis, rhinitis, Crohn's disease, ulcerative colitis, rheumatoid arthritis, osteoarthritis, migraine, cystitis and hypersensitivity reactions. Tachykinin antagonism may also be appropriate therapy for the treatment of pain, peripheral neuropathy, cough, emesis, post-herpetic neuralgia, adverse immunological reactions, blood flow disorders due to vasodilation, ophthalmic diseases, such as conjunctivitis and cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria and the like. Various central nervous system disorders including anxiety, depression, psychosis,

schizophrenia and dementia may also be amenable to treatment with tachykinin antagonists.

5 Asthma is a particular condition which may be treated with tachykinin antagonists. In experimental studies, sensory neuropeptides, especially tachykinins such as substance P and neurokinin A, can bring about many of the pathophysiological features of asthma. Neurokinin A
10 produces contraction of airway smooth muscle and increases airway responsiveness to other bronchoconstrictive stimuli. Although also contributing to bronchoconstriction in some species, substance P is more potent in its ability to cause mucus secretion,
15 microvascular leakage and vasodilation. Both tachykinins, substance P and neurokinin A, have been implicated in modulation of immune cells including mast cells, T lymphocytes, macrophages, eosinophils and neutrophils. The effectiveness of the combined NK₁ + NK₂ receptor
20 antagonist, FK 224, has been demonstrated in asthmatic patients undergoing bradykinin-induced bronchoconstriction by Ichinose et al. (Lancet (1992) Vol. 340: 1248-1251).

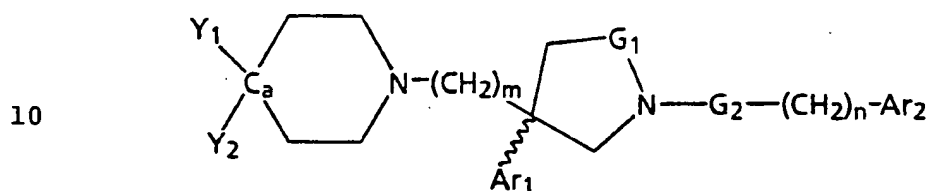
 The compounds of the present invention are novel. The
25 compounds of the present invention act as tachykinin antagonists and are thus potentially useful in the treatment of a number of diseases and conditions as described herein. A further object of the present invention is to provide a use for compounds,
30 stereoisomers, or pharmaceutically acceptable salts thereof, for the treatment or prevention of conditions and diseases in a patient in need thereof.

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SUMMARY OF THE INVENTION

The present invention relates to compounds of formula
 5 (1), their stereoisomers, and their pharmaceutically acceptable salts, and processes for preparing the same:



wherein

15 G_1 is $-\text{CH}_2-$ or $-\text{C}(\text{O})-$;

G_2 is $-\text{CH}_2-$ or $-\text{C}(\text{O})-$;

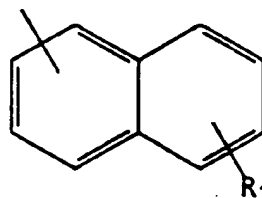
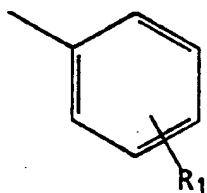
m is 2 or 3;

20

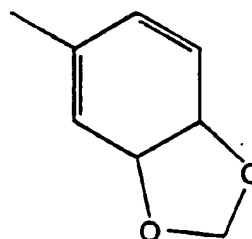
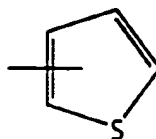
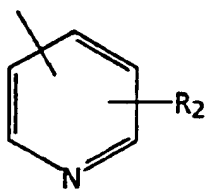
n is 0 or 1;

Ar_1 is a radical chosen from the group:

25



30



35

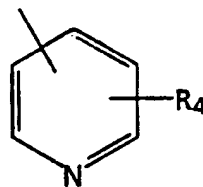
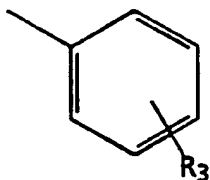
wherein

5 R_1 is from 1 to 3 substituents each independently chosen from the group consisting of hydrogen, halogen, hydroxy, CF_3 , C_1 - C_6 alkyl, and C_1 - C_6 alkoxy;

10 R_2 is from 1 to 2 substituents each independently chosen from the group consisting of hydrogen, halogen, C_1 - C_6 alkyl, and C_1 - C_6 alkoxy;

Ar_2 is a radical chosen from the group

15



20 wherein

R_3 is from 1 to 3 substituents each independently chosen from the group consisting of hydrogen, halogen, C_1 - C_6 alkyl, and C_1 - C_6 alkoxy;

25

R_4 is from 1 to 2 substituents each independently chosen from the group consisting of hydrogen, halogen, C_1 - C_6 alkyl, and C_1 - C_6 alkoxy;

30 Y_1 when selected individually is $-C(O)NHR_5$, $-C(O)NR_6R_7$, or $-C(O)NR_8R_9$

wherein

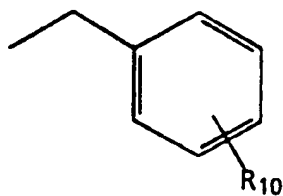
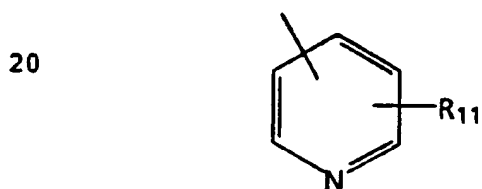
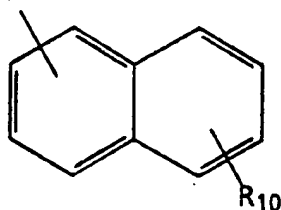
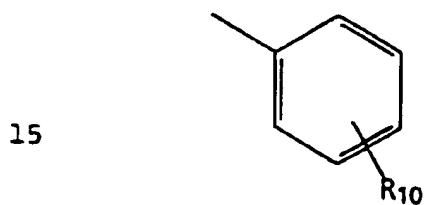
35 R_5 is chosen from the group consisting of hydrogen, C_1 - C_6 alkyl, 3-hydroxy-butyryl- C_1 - C_6 alkyl ester, glutar-2-yl- C_1 - C_6 alkyl ester, and $-CH_2CH_2N(CH_3)_2$;

R_6 is C_1 - C_6 alkyl;

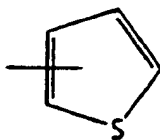
R₇ is C₁-C₆ alkyl;

- 5 R₈ and R₉ taken together with the bonded nitrogen form a morpholine ring, piperidine ring, 4-methylpiperazine ring, or pyrrolidine ring;

10 Y₂ when selected individually is a radical chosen from the group



25



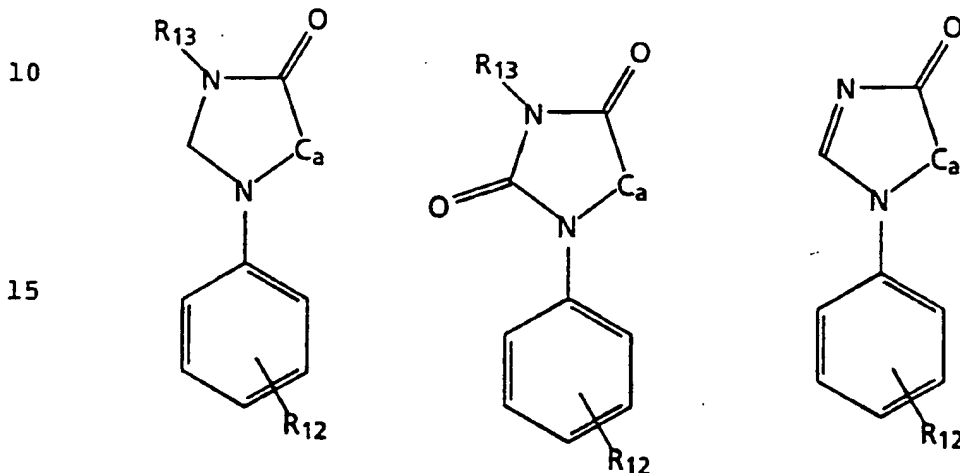
30

wherein

35 R₁₀ is from 1 to 3 substituents each independently chosen from the group consisting of hydrogen, halogen, CF₃, C₁-C₆ alkyl, and C₁-C₆ alkoxy;

R_{11} is from 1 to 2 substituents each independently chosen from the group consisting of hydrogen, halogen, C_1 - C_6 alkyl, and C_1 - C_6 alkoxy; or

Y_1 and Y_2 together with their attached carbon form a spirocyclic ring chosen from the group



wherein

the attached carbon is C_a ;

R_{12} is from 1 to 3 substituents each independently chosen from the group consisting of hydrogen, halogen, CF_3 , C_1 - C_6 alkyl, and C_1 - C_6 alkoxy;

R_{13} is hydrogen, C_1 - C_6 alkyl, or benzyl.

The present invention also provides a method of using the compounds of formula (1) therapeutically in a patient in need thereof, comprising administering a therapeutically effective amount of a compound of formula (1).

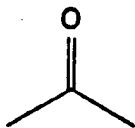
As is appreciated by one of ordinary skill in the art the compounds of the formula (1) may exist as stereoisomers depending on the nature of the substituents present. Any reference in this application to one of the compounds of the formula (1) is meant to encompass either specific stereoisomers or a mixture of stereoisomers. Where indicated, the compounds follow the designation of (+)- and (-)- for the stereochemistry of compounds represented by formula (1). It is also understood that the use of the term compounds of the formula (1) and the preferred embodiment thereof is also inclusive of all its stereoisomers, radicals, salts, and pharmaceutical formulations and compositions thereof. It is specifically recognized that in the substituted 2-(pyrrolidinyl-3-yl)-alkyl-piperidines the three position of the pyrrolidine is asymmetric, and may be in the (+)- or (-)- configuration, or may be a mixture thereof. The specific stereoisomers can be prepared by stereospecific synthesis or can be separated and recovered by techniques known in the art, such as chromatography on chiral stationary phases, enzymatic resolution, or fractional recrystallization of addition salts formed by reagents used for that purpose, as described in "Enantiomers, Racemates, and Resolutions", J. Jacques, A. Collet, and S. H. Wilen, Wiley (1981).


-10-

As used in this application:

- a) the term "halogen" refers to a fluorine atom, chlorine atom, bromine atom, or iodine atom;
- b) the term "C₁-C₆ alkyl" refer to a branched or straight chained alkyl radical containing from 1 to 4 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, pentyl, cyclopentyl, hexyl, cyclohexyl, etc;
- c) the term "C₁-C₆ alkoxy" refer to a straight or branched alkoxy group containing from 1 to 4 carbon atoms, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, t-butoxy, etc;
- d) the designations -C(O)- and -CO- refer to a carbonyl group of the formula:

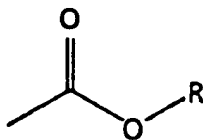
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- e) the designation "  " refers to a bond for which the stereochemistry is not designated;

- f) the designations -CO₂R and -C(O)OR refer to a group of the formula:

30

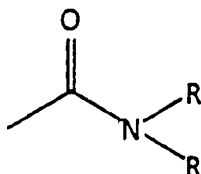


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-11-

g) the designation $-C(O)NRR$ refer to a group of the formula:

5

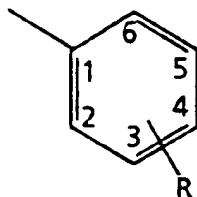


- h) as used in the examples and preparations, the following terms have the meanings indicated: "g" refers to grams, "mg" refers to milligrams, "mmol" refers to millimoles, "mL" refers to milliliters, "cm" refers to centimeters, "L" refers to liters, "°C" refers to degrees Celsius, "R_f" refers to retention factor, "mp" refers to melting point, "dec" refers to decomposition, "[α]_D²⁰" refers to specific rotation of the D line of sodium at 20° C obtained in a 1 decimeter cell, "c" refers to concentration in g/mL, "TFA" refers to trifluoroacetic acid, "THF" refers to tetrahydrofuran, "DMF" refers to dimethylformamide, "M" refers to molar, "μL" refers to microliters, "HPLC" refers to high performance liquid chromatography, "eq." refers to equivalents; h refers to hours; "N" refers to normal, "X" refers to times, "NaHMDS" refers to sodium hexamethyldisilazide or sodium bis-(trimethylsilyl)amide, "EBA" refers to ethyl bromoacetate, "LiAlH₄" refers to lithium aluminum hydride, "NMM" refers to 4-methylmorpholine, "aryl₁" refers to Ar₁, "aryl₂" refers to Ar₂, "Boc" or t-BOC" refers to t-butyloxycarbonyl; "EDC" refers to 1-(3-dimethyl aminopropyl)-3-ethylcarbodiimide hydrochloride; "HOBT" or "HOBT" refers to 1-hydroxybenzotriazole hydrate, "R_t" refers to retention time, "K₂CO₃" refers to potassium carbonate, "Na₂SO₄" refers to sodium sulfate, "MgSO₄" refers to magnesium sulfate, "H₂O" refers to water, "SOCl₂" refers to thionyl chloride, "NaOH" refers to sodium hydroxide, "CH₃CN" refers to acetonitrile, "KOH" refers to potassium hydroxide;

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i) the designation

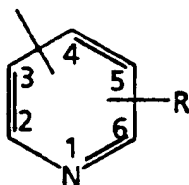
5



10 refers to a phenyl or substituted phenyl and it is understood that the radical is attached at the 1-position and the substituent or substituents represented by R can be attached in any of the 2, 3, 4, 5, or 6 positions;

15 j) the designation

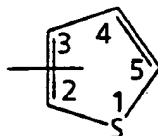
20



refers to a pyridine, substituted pyridine, pyridinyl, or substituted pyridinyl and it is understood that the radical
25 can be attached at the either the 2-position, the 3-position, or the 4-position, it is further understood that when the radical is attached at the 2-position the substituent or substituents represented by R can be attached in any of the 3, 4, 5, or 6, positions, that when the
30 radical is attached at the 3-position the substituent or substituents represented by R can be attached in any of the 2, 4, 5, or 6 positions, and that when the radical is attached at the 4-position the substituent or substituents represented by R can be attached in any of the 2, 3, 5, or 6
35 positions;

k) the designation

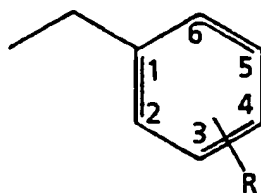
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10 refers to a thienyl, thiophene, or thiophenyl and it is understood that the radical is attached at the 2- or the 3-positions;

l) the designation

15



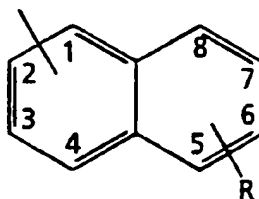
20

refers to a benzyl or substituted benzyl and it is understood that the substituent or substituents represented by R can be attached in any of the 2, 3, 4, 5, or 6 positions;

25

m) the designation

30



35

refers to a naphthyl, substituted naphthyl, naphthalenyl, substituted naphthalenyl and it is understood that the radical can be attached at the either the 1-position or the 2-position, it is further understood that when the radical

is attached at the 1-position the substituent or substituents represented by R can be attached in any of the 2, 3, 4, 5, 6, 7, or 8 positions and that when the radical 5 is attached at the 2-position the substituent or substituents represented by R can be attached in any of the 1, 3, 4, 5, 6, 7, or 8 positions;

n) the term "pharmaceutically acceptable salts thereof" refers to either an acid addition salt or a basic addition salt.

o) the term "enantiomeric excess" or "ee" refers to the percent by which one enantiomer, E1, is in excess in a mixture of the two enantiomers, E1 plus E2, such that;

$$\frac{(E1 - E2)}{(E1 + E2)} \times 100\% = ee$$

The term (+)- refers to the plus enantiomer, (-)- refers to the minus enantiomer.

The expression "pharmaceutically acceptable acid addition salts" is intended to apply to any non-toxic organic or inorganic acid addition salt of the base compounds represented by formula (1) or any of its intermediates. Illustrative inorganic acids which form suitable salts include hydrochloric, hydrobromic, sulphuric, and phosphoric acid and acid metal salts such as sodium monohydrogen orthophosphate, and potassium hydrogen sulfate. Illustrative organic acids which form suitable salts include the mono-, di-, and tricarboxylic acids. Illustrative of such acids are for example, acetic, glycolic, lactic, pyruvic, malonic, succinic, glutaric, fumaric, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, benzoic, hydroxy-benzoic, phenylacetic, cinnamic, salicylic, 2-phenoxy-benzoic, p-toluenesulfonic acid, and sulfonic acids such as methane sulfonic acid and 2-hydroxyethane sulfonic acid. Such salts can exist in either a hydrated or

substantially anhydrous form. In general, the acid addition salts of these compounds are soluble in water and various hydrophilic organic solvents, and which in comparison to their free base forms, generally demonstrate higher melting points.

The expression "pharmaceutically acceptable basic addition salts" is intended to apply to any non-toxic organic or inorganic basic addition salts of the compounds represented by formula (1) or any of its intermediates. Illustrative bases which form suitable salts include alkali metal or alkaline-earth metal hydroxides such as sodium, potassium, calcium, magnesium, or barium hydroxides; ammonia, and aliphatic, alicyclic, or aromatic organic amines such as methylamine, dimethylamine, trimethylamine, and picoline. Either the mono- or di-basic salts can be formed with those compounds.

Preferred embodiments of formula (1) are given below:

- 1) When Y_1 and Y_2 are chosen independently, a preferred embodiment is where Y_1 is chosen to be $-C(O)NHR_5$;
- 2) When Y_1 and Y_2 are chosen independently a preferred embodiment is where Y_2 is chosen to be phenyl or substituted phenyl;
- 3) A preferred embodiment is when m is 2;
- 4) A preferred embodiment is when n is 0;
- 5) A preferred embodiment is when G_1 is $-CH_2-$ and G_2 is $-C(O)-$;
- 6) A preferred embodiment is when G_1 is $-C(O)-$ and G_2 is $-CH_2-$.

It is understood that further preferred embodiments of formula (1) can be selected by requiring one or more of the preferred embodiments above.

5

Nomenclature of the titled compounds of the invention were generated in part with the AUTONOM program, Version 1.0, of the Beilstein Institute, distributed by Springer-Verlag, Heidelberg (Copyright 1990, 1991) which are
10 illustrated in Table 1 with their AUTONOM generated name and corresponding example number for several of the examples.

TABLE 1

15

20

25

30

35

Example #	General Nomenclature
9	8-[2-[3-(3,4-dichloro-phenyl)-1-(2,6-dimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-1-phenyl-1,3,8-triaza-spiro[4.5]decane-4-one
3	1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide
5	1-[2-[3-(3,4-dichloro-phenyl)-1-(2,6-dimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide
4	1-(2-[3-(3,4-dichloro-phenyl)-1-[2-(2-methoxy-phenyl)-acetyl]-pyrrolidin-3-yl]-ethyl)-4-phenyl-piperidine-4-carboxylic acid amide
13	1-[2-[3-(3,4-dichloro-phenyl)-1-(2-methoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide
2	1-[2-[3-(3,4-dichloro-phenyl)-1-(2,4-dimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide
6	2-[(2-[1-benzoyl-3-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethyl)-4-phenyl-piperidine-4-carboxyl)-amino]-pentanedioic acid dimethyl ester
11	1-[2-[1-benzyl-3-(3,4-dichloro-phenyl)-5-oxo-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide
1	1-[2-[3-(3,4-dichloro-phenyl)-1-benzoyl-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide

TABLE 1

Example #	General Nomenclature
10	8-[2-[3-(3,4-dichloro-phenyl)-1-benzoyl-pyrrolidin-3-yl]-ethyl]-1-phenyl-1,3,8-triaza-spiro[4.5]-decane-4-one
7	2-[(1-(2-[1-benzoyl-3-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethyl)-4-phenyl-piperidine-4-carboxyl)-amino]-3-hydroxy butyric acid methyl ester
12	1-[1-benzyl-3-naphthalen-2-yl-5-oxo-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide
8	1-[2-(1-benzoyl-3-naphthalen-2-yl-pyrrolidin-3-yl)-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide
20	(+)-1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide
21	(-)-1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide
23	1-[2-[3-(3,4-dimethoxy-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide
24	1-[2-[3-(3,4-dichloro-phenyl)-1-(3,5-bis-(trifluoromethyl)-pyrrolidin-3-yl)-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide
25	1-[2-[3-(3,4-dichloro-phenyl)-1-(3,5-dimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide
26	1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid (2-dimethylamino-ethyl)-amide
27	1-[2-[3-(3,4-dichloro-phenyl)-1-(3-methoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide
22	1-[2-[3-phenyl-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide

Illustrative Examples of compounds encompassed by the present invention include:

- 5 8-[2-[3-(3,4-dichloro-phenyl)-1-(2,6-dimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-1-phenyl-1,3,8-triaza-spiro[4.5]decane-4-one;
- 10 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide;
- 15 1-[2-[3-(3,4-dichloro-phenyl)-1-(2,6-dimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide;
- 20 1-(2-[3-(3,4-dichloro-phenyl)-1-[2-(2-methoxy-phenyl)-acetyl]-pyrrolidin-3-yl]-ethyl)-4-phenyl-piperidine-4-carboxylic acid amide;
- 25 1-[2-[3-(3,4-dichloro-phenyl)-1-(2,4-dimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide;
- 30 2-[(2-[1-benzoyl-3-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethyl)-4-phenyl-piperidine-4-carbonyl]-amino]-pentanedioic acid dimethyl ester;
- 35 1-[2-[1-benzyl-3-(3,4-dichloro-phenyl)-5-oxo-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide;
- 1-[2-[3-(3,4-dichloro-phenyl)-1-benzoyl-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide;

- 8-[2-[3-(3,4-dichloro-phenyl)-1-benzoyl-pyrrolidin-3-yl]-ethyl]-1-phenyl-1,3,8-triaza-spiro[4.5]-decane-4-one;
- 5 2-[(1-(2-[1-benzoyl-3-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethyl)-4-phenyl-piperidine-4-carboxyl)-amino]-3-hydroxy butyric acid methyl ester;
- 1-[1-benzyl-3-naphthalen-2-yl-5-oxo-pyrrolidin-3-yl-ethyl]-
10 4-phenyl-piperidine-4-carboxylic acid amide;
- 1-[2-(1-benzoyl-3-naphthalen-2-yl-pyrrolidin-3-yl)-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide;
- 15 (+)-1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide;
- (-)-1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide;
20
- 1-[2-[3-phenyl-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide;
25
- 1-[2-[3-(3,4-dimethoxy-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide;
- 30 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,5-bis-(trifluoromethyl)-pyrrolidin-3-yl)-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide;
- 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid (2-dimethylamino-ethyl)-amide;
35

1-[2-[3-(3,4-dichloro-phenyl)-1-(3-methoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide;

5

1-[2-[3-(benzo[1,3]dioxol-5-yl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide;

10 1-[2-[3-(3,4-dimethoxy-phenyl)-1-(3,4,5-triethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide;

15 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-(naphth-2-yl)-piperidine-4-carboxylic acid amide;

20 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-(pyridin-4-yl)-piperidine-4-carboxylic acid amide;

25 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-(pyridin-3-yl)-piperidine-4-carboxylic acid amide;

1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-(pyridin-2-yl)-piperidine-4-carboxylic acid amide;

30 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-benzyl-piperidine-4-carboxylic acid amide;

35 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid pyrrolidine-amide;

- 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,5-dimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide
- 5 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid morpholine-amide;
- 10 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid piperidine-amide;
- 15 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid methyl-amide;
- 20 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid dimethyl-amide;
- 25 1-[2-[3-(3,4-dichloro-phenyl)-1-(4-chloro-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide;
- 30 1-[2-[3-(3,4-dichloro-phenyl)-1-(4-*tert*-butyl-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide;
- 35 1-[2-[3-(3,4-dichloro-phenyl)-1-(3-isopropoxy-phenacyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide;

- 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-phenacyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide;
- 5 1-[2-[3-(3,4-dichloro-phenyl)-1-(pyridine-2-carbonyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide;
- 10 8-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one;
- 8-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]dec-2-en-4-one;
- 15 8-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one
- 20 3-benzyl-8-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one;
- 25 3-benzyl-8-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decane-2,4-dione;
- 30 8-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decane-2,4-dione;
- 1-[2-[3-(3-trifluoromethyl-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide;
- 35

1-[2-[3-(thiophen-2-yl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide;

5

1-[2-[3-(pyridin-3-yl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide;

10 1-[2-[3-(2-fluoro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide;

15 1-[2-[3-(4-hydroxy-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide;

20 1-[2-[3-(4-trifluoromethyl-phenyl)-1-(3-isopropoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide;

25 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-(thiophen-2-yl)-piperidine-4-carboxylic acid amide;

1-[2-[3-(3,4-dichloro-phenyl)-5-oxo-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide;

30 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide;

35 1-[3-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-propyl]-4-phenyl-piperidine-4-carboxylic acid amide;

1-[3-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzyl)-pyrrolidin-3-yl]-propyl]-4-phenyl-piperidine-4-carboxylic acid amide;

5

1-[3-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzyl)-5-oxo-pyrrolidin-3-yl]-propyl]-4-phenyl-piperidine-4-carboxylic acid amide;

10 1-[3-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-5-oxo-pyrrolidin-3-yl]-propyl]-4-phenyl-piperidine-4-carboxylic acid amide;

15 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,5-dimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide.

20

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REACTION SCHEMES

5 Compounds of formula (1) and intermediates thereof can be prepared as described in the Reaction Schemes A through M below. All the substituents, unless otherwise indicated, are previously defined. The reagents and starting materials are readily available to one of ordinary skill in the art.

10

Reaction Scheme A

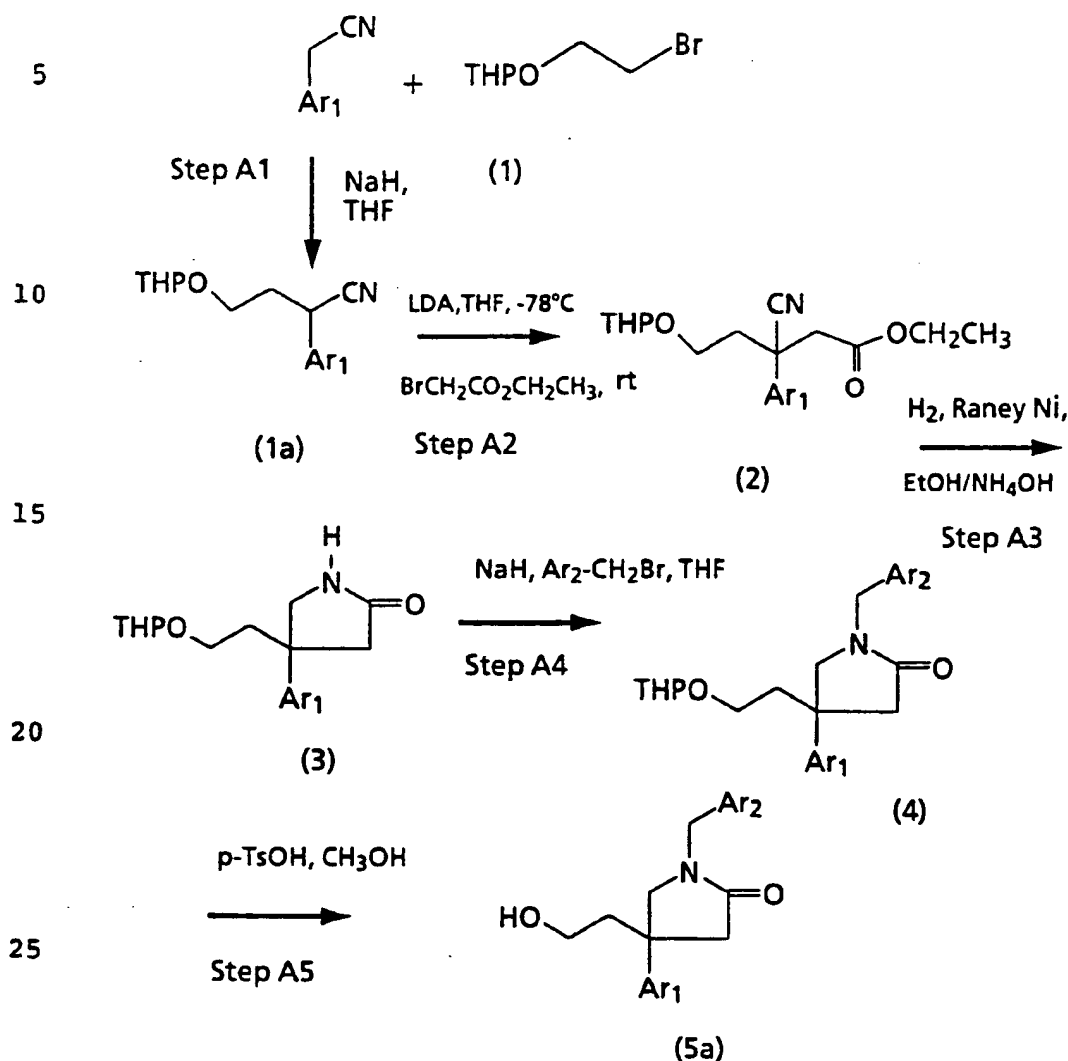
Reaction Scheme A may be used to synthesize substituted 1-aralkyl-3-aryl-3-(2-hydroxyethyl)-5-oxo-pyrrolidine as
15 shown in formula 5a (see scheme A on next page). The substituents of formula 5a, 1-aralkyl-3-aryl-3-(2-hydroxyethyl)-pyrrolidines, are defined such that Ar₁ and Ar₂ are as desired in the final product.

20 In reaction Scheme A, Step A1, alkylation of the aryl-acetonitrile may be accomplished with 2-(2-bromo-ethoxy)-tetrahydro-pyran to form the 2-aryl-4-(tetrahydro-pyran-2-yloxy)-butyronitrile which is then followed by a second alkylation with ethyl bromoacetate (step A2) to form the 3-
25 cyano-3-aryl-5-(tetrahydro-pyran-2-yloxy)-pentanoic acid ethyl ester (compound 2).

The 3-cyano-3-aryl-5-(tetrahydro-pyran-2-yloxy)-pentanoic acid ethyl ester is able to be converted to the
30 corresponding lactam by reduction, as is illustrated by treatment with hydrogen and Raney nickel (step A3) to form the corresponding 4-aryl-4-[2-(tetrahydro-pyran-2-yloxy)ethyl]-pyrrolidin-2-one (compound 3).

35 The selected aralkyl group having the desired substituents previously defined for formula 5a, may be added to pyrrolidine ring nitrogen by alkylation with an aralkyl halide, such as benzyl bromide, (step A4) to form

Reaction Scheme A



the corresponding 1-aralkyl-4-aryl-4-[2-(tetrahydro-pyran-2-yloxy)ethyl]-pyrrolidin-2-one.

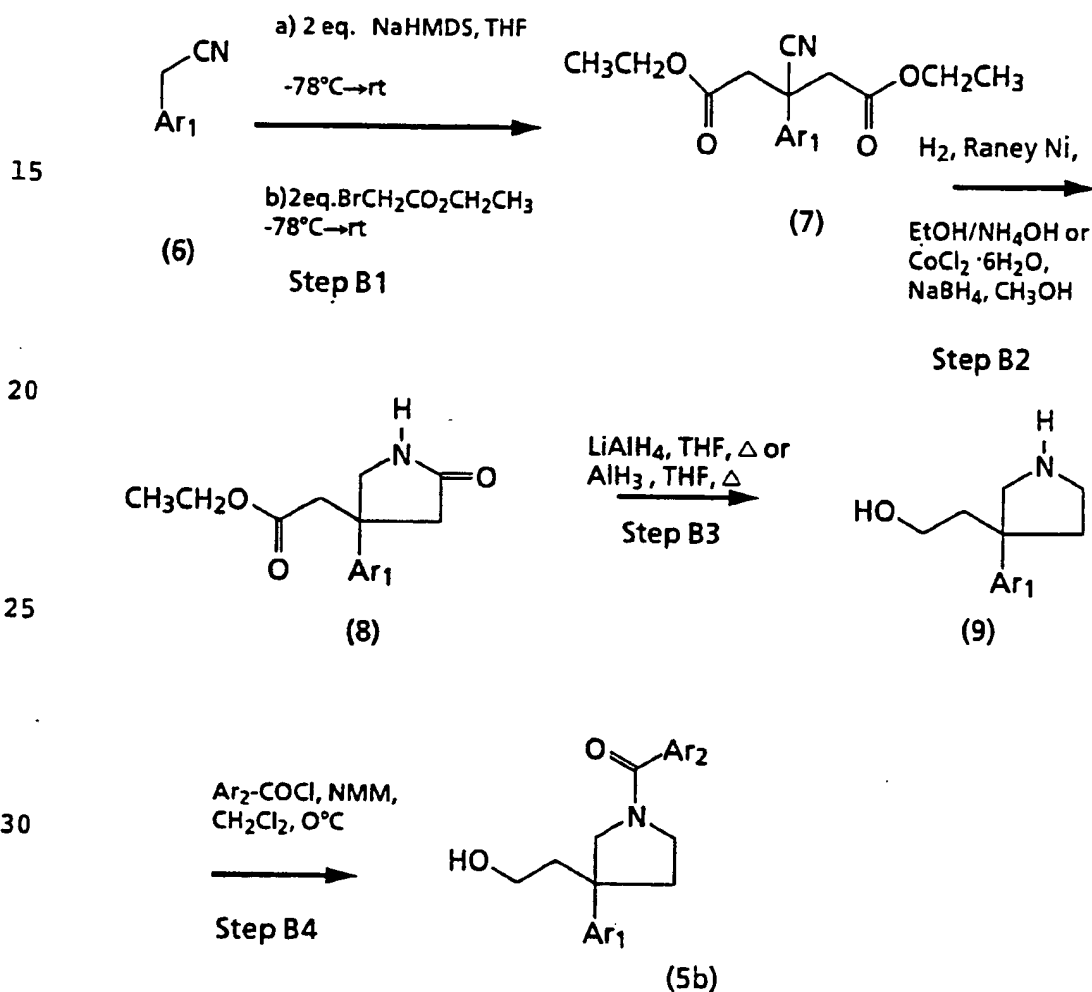
The 5(a) intermediate corresponding to the 1-aralkyl-4-aryl-4-(2-hydroxyethyl)-pyrrolidin-2-one may be obtained by removal of the tetrahydropyran group by treatment of compound 4 with a suitable acid, such as p-toluenesulfonic acid in methanol.

Reaction Scheme B

Reaction Scheme B may be used to synthesize
 5 intermediate compounds wherein the structure is a
 substituted 1-aryl-3-aryl-3-(2-hydroxyethyl)-pyrrolidine,
 as shown in formula 5b, or a substituted 1-arylacetyl-3-
 aryl-3-(2-hydroxyethyl)-pyrrolidine.

Reaction Scheme B

10



35 The compounds of formula 5b, 1-aryl-3-aryl-3-(2-hydroxy-
 ethyl)-pyrrolidines and 1-phenylacetyl-3-aryl-3-(2-
 hydroxyethyl)-pyrrolidines are defined such Ar₁ and Ar₂ are
 as desired in the final product.

In reaction Scheme B, Step B1, the aryl-acetonitrile is treated with a base, for example, sodium bis (trimethylsilyl)amide), followed by addition of ethyl
5 bromoacetate to produce the 3-cyano-3-aryl-pentanedioic diethyl ester (compound 7).

The 3-cyano group of the 3-cyano-3-aryl-pentanedioic diethyl ester may then subsequently be reduced with an
10 appropriate reducing reagent (step B2), for example Raney nickel and hydrogen or with cobalt (II) chloride and sodium borohydride to give the corresponding 3-aryl-5-oxo-pyrrolidin-3-yl]-acetic acid ethyl ester (compound 8).

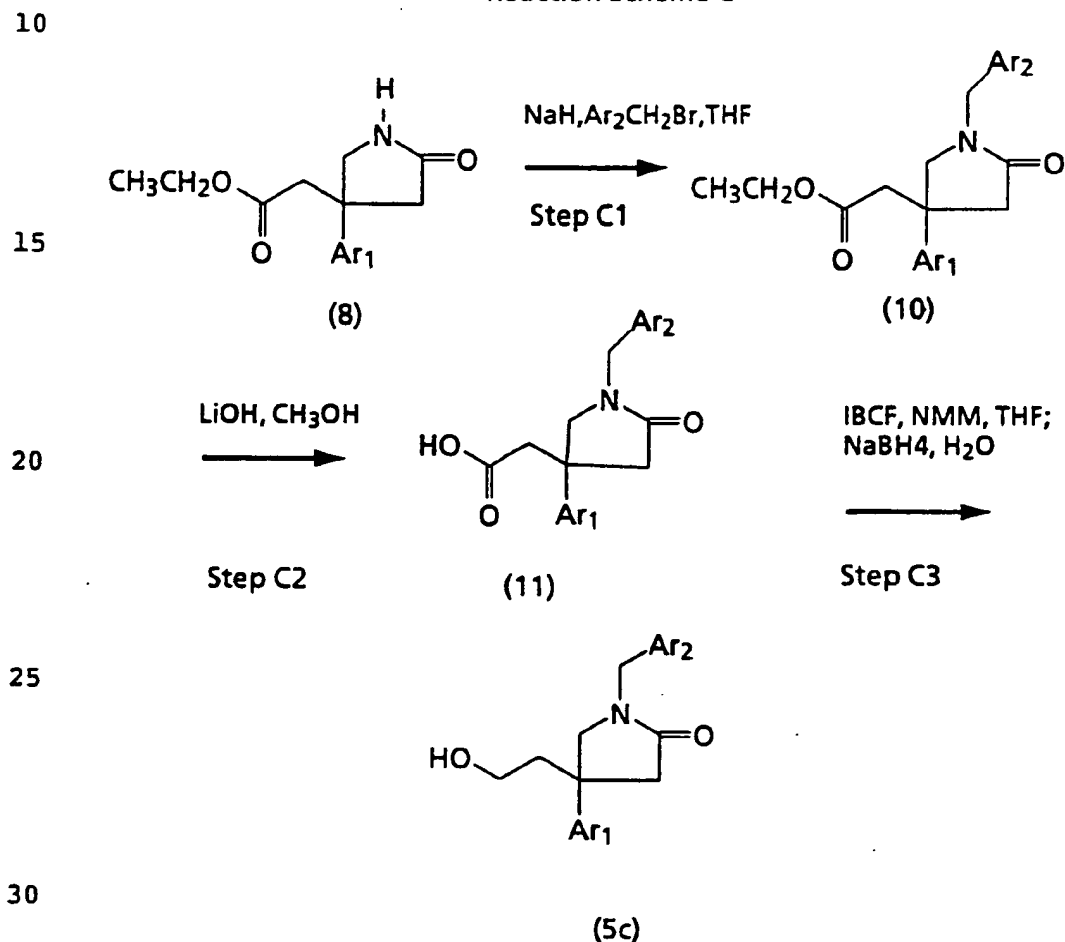
15 The 3-aryl-5-oxo-pyrrolidin-3-yl-acetic acid ethyl ester (compound 8) may subsequently be used in Scheme C or the 5-oxo-pyrrolidine ring may be reduced (step B3) with an appropriate reducing reagent, such as lithium aluminum hydride or aluminum hydride, to form the corresponding 3-
20 aryl-3-(2-hydroxyethyl)-pyrrolidine (compound 9).

The pyrrolidine of compound 9 may subsequently be aroylated with an appropriately substituted benzoyl chloride in the presence of base such as 4-methylmorpholine
25 to form the corresponding 1-aroyle-3-aryl-3-(2-hydroxyethyl)-pyrrolidine (Compound 5b) or substituted with an appropriately substituted with a substituted arylacetyl chloride or aroyl chloride to form the corresponding 1-arylacetyl-3-aryl-3-(2-hydroxyethyl)-pyrrolidine or 1-
30 aroyl-3-aryl-3-(2-hydroxyethyl)-pyrrolidine.

Reaction Scheme C

Reaction Scheme C is an alternative route which may be used to synthesize intermediate compounds wherein the structure is a substituted 1-aralkyl-3-aryl-3-(2-hydroxyethyl)-5-oxo-pyrrolidine as shown in formula 5a.

Reaction Scheme C



The substituents of formula 5a, 1-aralkyl-3-aryl-3-(2-hydroxyethyl)-pyrrolidines, have been previously defined wherein Ar_1 and Ar_2 are as desired in the final product.

A selected group from aryl may be added to the pyrrolidine ring of the (3-aryl-5-oxo-pyrrolidin-3-yl)-acetic acid ethyl ester (compound 8) by alkylation (step

Cl) of the nitrogen of pyrrolidine with an aralkyl halide, such as benzyl bromide, for example, to form the corresponding 1-aralkyl-3-aryl-5-oxo-pyrrolidin-3-yl-acetic acid ethyl ester (compound 10).

Conversion of the ethyl ester of compound 10 to the corresponding acid of compound 11 may be accomplished by base hydrolysis, for example lithium hydroxide in methanol, to form the 1-aralkyl-3-aryl-5-oxo-pyrrolidin-3-yl-acetic acid (compound 11).

The acetic acid of compound 11 is subsequently able to be reduced, for example, via the corresponding mixed anhydride in the presence of sodium borohydride to form the 1-aralkyl-4-aryl-4-(2-hydroxyethyl)-pyrrolidin-2-ones shown (compound 5c).

20

25

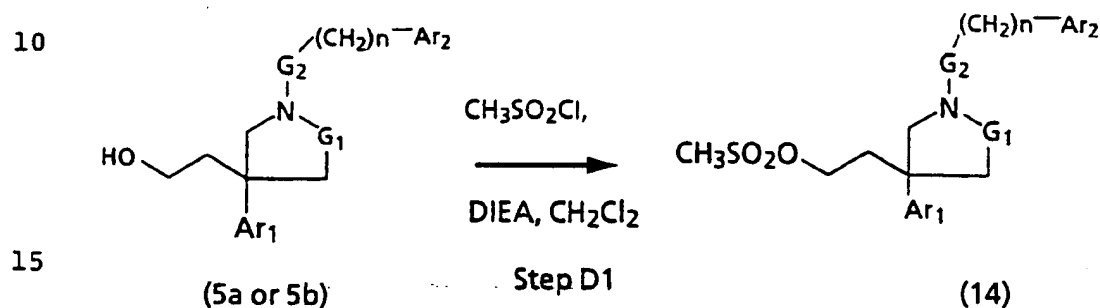
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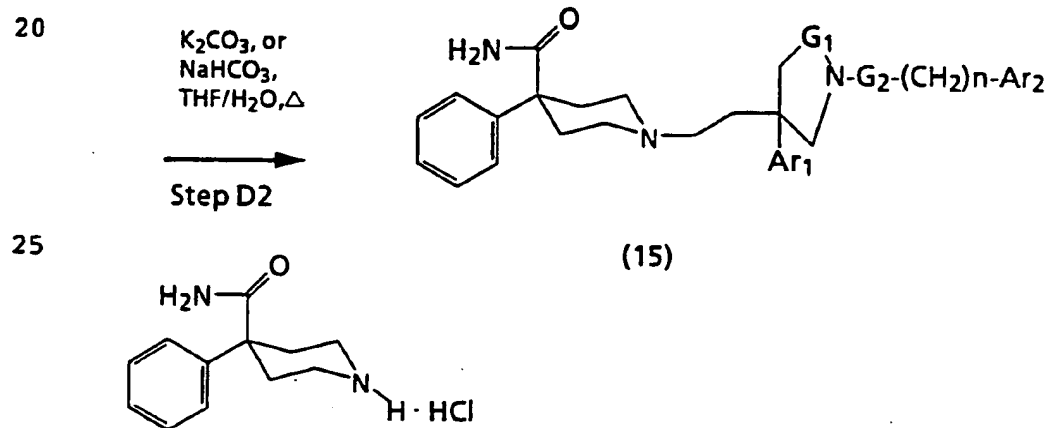
Reaction Scheme D

Reaction Scheme D may be used to synthesize the aryl
 5 substituted 2-(pyrrolidin-3-yl)-ethyl-piperidines of the
 invention.

Reaction Scheme D



G₁ and G₂ may be -CH₂- and -CO-
 or -CO- and -CH₂- respectively
 n = 0 or 1



Scheme D is a general type procedure for condensation of
 substituted piperidines with substituted 1-aralkyl-3-aryl-
 3-(2-hydroxyethyl)-pyrrolidines, substituted 1-aroyle-3-
 35 arylacetyl-3-(2-hydroxyethyl)-pyrrolidine, or substituted
 1-aroyle-3-aryl-3-(hydroxyethyl)-pyrrolidines previously
 discussed in Schemes A (Compound 5a), B (Compound 5b), or C
 (Compound 5c). The compounds of formula 15 are derived
 from the starting compounds described for Compounds 5a, 5b,

and 5c, wherein the Ar₁ and Ar₂ is as desired in the final product.

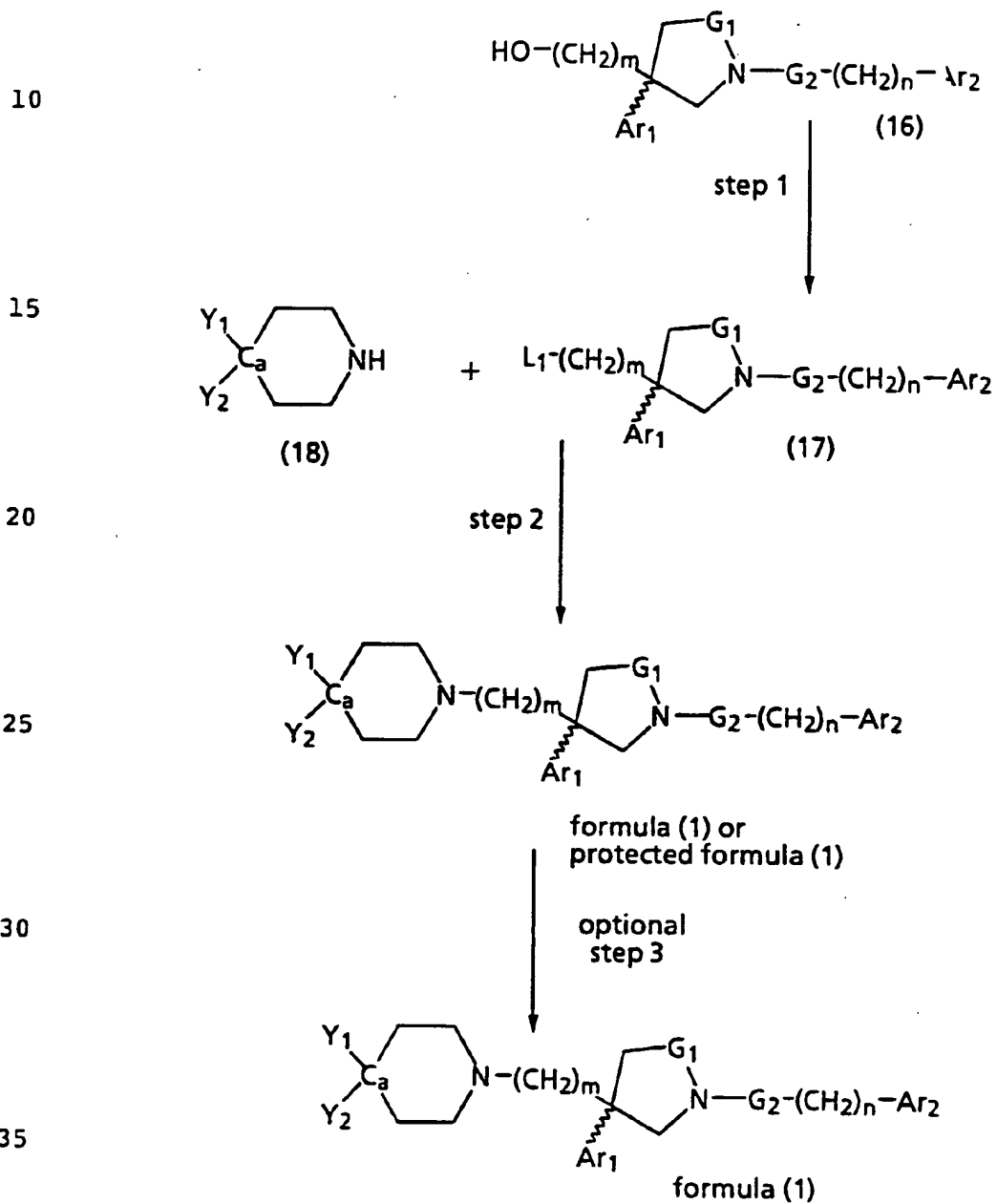
5 Conversion of 1-alkyl-3-aryl-3-(2-hydroxyethyl)-pyrrolidines, 1-arylacetyl-3-aryl-3-(2-hydroxyethyl)-pyrrolidines, or 1-aroyl-3-aryl-3-(2-hydroxyethyl)-pyrrolidines of intermediates 5a, 5b, or 5c may be accomplished by converting the 2-hydroxyethyl group to the
10 corresponding mesylate by allowing 5a or 5b to react with methanesulfonyl chloride (step D1) and then allowing the mesylate derivative to react with a piperidine derivative to form the titled aryl substituted 2-(pyrrolidin-3-yl)-ethyl-piperidines of formula 15. It is realized that
15 although the 4-phenyl-piperidine-4-carboxylic acid amide is shown as the substituted piperidine it may be replaced by a number of other piperidines or substituted piperidines. For instance, the piperidine derivatives may be condensed with the 1-aroyl-3-aryl-3-(2-hydroxy-ethyl)-pyrrolidine by
20 refluxing the compounds in THF/water with a weak base, such as sodium bicarbonate or potassium carbonate. Suitable piperidine derivatives for condensation include, but are not limited to 4-phenyl-piperidine-4-carboxylic acid amide (4-phenyl isonipecotamide), 1-phenyl-1,3,8-triaza-
25 spiro[4.5]decan-4-one, and the like.

 The piperidine derivative can be further reacted following condensation with the mesylate. For example, one can use the 4-phenyl-piperidine-4-carboxylic acid methyl
30 ester in the condensation with the mesylate derived from a 3-hydroxy-ethyl-pyrrolidine. After condensation of the piperidine derivative with the mesylate the 4-carboxylic acid ester protecting group may be removed to afford an intermediate acid derivative and further reacted to form
35 the appropriate alkyl amides.

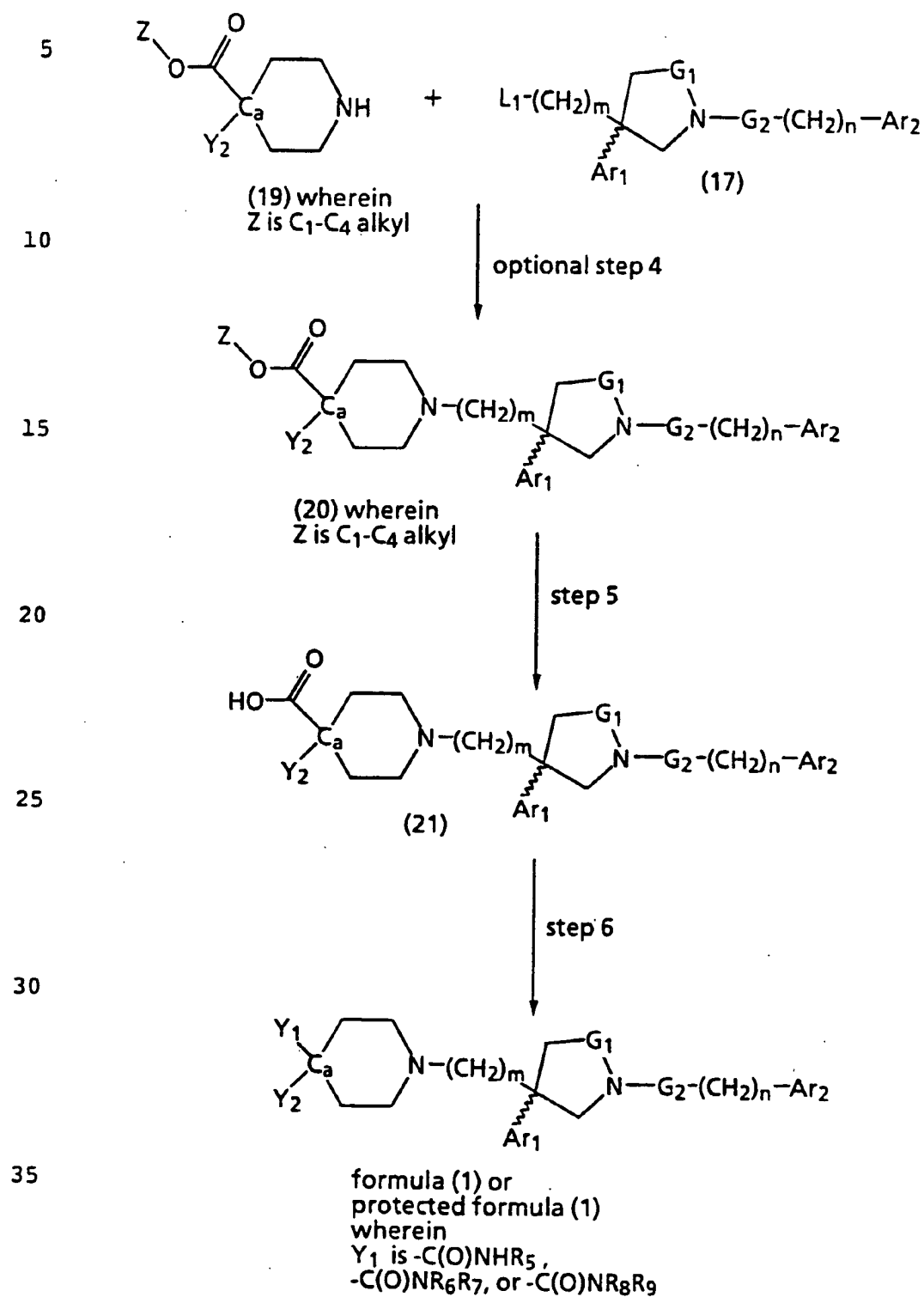
Reaction Scheme E

Reaction Scheme E is a general scheme for preparing the 5 compounds of formula (1).

Reaction Scheme E



Reaction Scheme E (Cont.)



- In Reaction Scheme E, step 1, the hydroxy group of an appropriate 3-(ω -hydroxyalkyl)pyrrolidine compound of formula 16 is converted to an appropriate leaving group.
- 5 An appropriate 3-(ω -hydroxyalkyl)pyrrolidine compound of formula 16 is one in which m, n, G₁, G₂, Ar₁ and Ar₂ are as desired in the final product of formula (1) or can be one in which Ar₁ gives rise after deprotection to a group Ar₁ as desired in the final product of formula (1). An
- 10 appropriate leaving group, L₁, is one which can be displaced by a piperidine of formula 18 to give a compound of formula (1). Appropriate leaving groups, L₁, include but are not limited to chloro, bromo, iodo, mesylate, tosylate, benzenesulfonate, trifluoromethanesulfonate, and the like.
- 15 The conversion of hydroxy groups to leaving groups such as chloro, bromo, iodo, mesylate, tosylate, benzenesulfonate, and trifluoromethanesulfonate is well known and appreciated in the art.
- 20 For example, compounds in which L₁ is bromo are formed by contacting an appropriate 3-(ω -hydroxyalkyl)pyrrolidine compound of formula 16 with 1.0 to 1.5 molar equivalents of carbon tetrabromide and 1.0 to 1.75 molar equivalents
- 25 triphenylphosphine. (P. J. Kocienski et al. JOC 42, 353-355 (1977)). The reaction is carried out by combining the 3-(ω -hydroxyalkyl)pyrrolidine compound of formula 16 with carbon tetrabromide in a suitable solvent, such as dichloromethane or chloroform and then adding a solution of triphenylphosphine in a suitable solvent, such as
- 30 dichloromethane or chloroform. Generally the reaction is carried out at temperatures of from -10°C to ambient temperature. Generally, the reactions require from 5 minutes to 24 hours. The product can be isolated and purified by techniques well known in the art, such as
- 35 extraction, evaporation, trituration, chromatography, and recrystallization.

Compounds in which L₁ is bromo are also formed by contacting an appropriate 3-(ω-hydroxyalkyl)pyrrolidine compound of formula 16 with a slight molar excess of triphenylphosphine dibromide. (R. F Borch et al. JACS 99, 1612-1619 (1977)). The reaction may be carried out by contacting an appropriate 3-(ω-hydroxyalkyl)pyrrolidine compound of formula 16 with preformed triphenylphosphine dibromide. The reaction is carried out in a suitable solvent, such as tetrahydrofuran and diethyl ether. The reaction is carried out in the presence of a suitable base, such as pyridine. Generally the reaction is carried out at temperatures of from 0°C to 50°C. Generally, the reactions require from 5 minutes to 24 hours. The product can be isolated and purified by techniques well known in the art, such as extraction, evaporation, trituration, chromatography, and recrystallization.

Alternately, for example, compounds in which L₁ is mesylate are formed by contacting an appropriate 3-(ω-hydroxyalkyl)pyrrolidine compound of formula 16 with a molar excess of methanesulfonyl chloride. The reaction is carried out in a suitable solvent, such as dichloromethane, chloroform, toluene, benzene, or pyridine. The reaction is carried out in the presence of a suitable base, such as triethylamine, diisopropylethyl amine, or pyridine. Generally the reaction is carried out at temperatures of from -20°C to 50°C. Generally, the reactions require from 1 hour to 24 hours. The product can be isolated and purified by techniques well known in the art, such as extraction, evaporation, trituration, chromatography, and recrystallization.

Compounds of formula 17 in which L₁ is iodo can be prepared from compounds of formula 17 in which L₁ is mesylate, chloro, or bromo by an exchange reaction, such as the Finkelstein reaction.

For example, a compound of formula 17 in which L₁ is mesylate, chloro, or bromo is contacted with from 1.0 to 10.0 molar equivalents of an iodide salt, such as sodium iodide or potassium iodide. The reaction is carried out in a suitable solvent, such as acetone or butanone. Generally, the reaction is carried out at temperatures of from ambient temperature to the refluxing temperature of the solvent. Generally, the reactions require from 1 hour to 24 hours. The product can be isolated and purified by techniques well known in the art, such as extraction, evaporation, trituration, chromatography, and recrystallization.

In Reaction Scheme E, step 2, an appropriate 3-(ω-L₁-alkyl)pyrrolidine compound of formula 17 reacts with an appropriate piperidine compound of formula 18 or salt of an appropriate piperidine of formula 18 to give a protected compound of formula (1) or a compound of formula (1). An appropriate compound of formula 17 is one in which the leaving group, L₁, is one which can be displaced by a piperidine of formula 18, m, n, G₁, G₂, Ar₁ and Ar₂ are as desired in the final product of formula (1) or can be one in which Ar₁ gives rise after deprotection to a group Ar₁ as desired in the final product of formula (1). An appropriate piperidine of formula 18 or salt of an appropriate piperidine of formula 18 is one in which Y₁ and Y₂ are as desired in the final product of formula (1).

For example, an appropriate 3-(ω-L₁-alkyl)pyrrolidine compound of formula 17 is contacted with an appropriate piperidine compound of formula 18 or salt of an appropriate piperidine of formula 18 to give a protected compound of formula (1) or a compound of formula (1). The reaction is carried out in a suitable solvent, such as tetrahydrofuran, tetrahydrofuran/water mixtures, pyridine, acetonitrile, toluene, toluene/water mixtures, or dimethylformamide. The reaction is carried out in the presence of from 1.0 to 6.0

molar equivalents of a suitable base, such as sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine, pyridine, or
5 diisopropylethylamine. When a salt of an appropriate piperidine of formula 18 is used, an additional molar excess of a suitable base is used. The reaction may be facilitated by the addition of a catalytic amount, 0.1 to 0.5 molar equivalents, of an iodide salt, such as sodium
10 iodide or potassium iodide. The reaction is generally carried out at temperatures of from ambient temperature to the refluxing temperature of the solvent. Generally, the reactions require 1 to 72 hours. The product can be isolated and purified by techniques well known in the art,
15 such as extraction, evaporation, trituration, chromatography, and recrystallization.

In Reaction Scheme E, optional step 3, a protected compound of formula (1) is deprotected to give a compound
20 of formula (1). A deprotection reaction, such as the removal of hydroxy protecting groups utilizing suitable protecting groups such as those described in Protecting Groups in Organic Synthesis by T. Greene is well known and appreciated in the art.

25

Alternately, the compounds of formula (1) can be prepared by forming the amide group after the formation of an appropriate carboxylic acid derivative as generally taught below.

30

In Reaction Scheme E, optional step 4, an appropriate compound of formula 17, as defined above is contacted with an appropriate piperidine ester of formula 19 or salt of an appropriate piperidine ester of formula 19. An appropriate
35 piperidine ester of formula 19 or salt of an appropriate piperidine ester of formula 19 is one in which Y_2 is as desired in the final product of formula (1) and Z is a C_1-C_4

alkyl group. This step is carried out as generally taught in Reaction Scheme E, step 2.

- 5 In Reaction Scheme E, step 5, an appropriate ester of formula 20 is hydrolyzed to give an acid of formula 21.

For example, an appropriate ester of formula 20 is contacted with a suitable hydrolyzing agent, such as sodium
10 hydroxide, potassium hydroxide, or lithium hydroxide. The reaction is carried out in a suitable solvent such as water, tetrahydrofuran/water mixtures, methanol, methanol/water mixtures, or ethanol/water mixtures. The reaction is generally carried out at temperatures of from
15 0°C to the refluxing temperature of the solvent. Generally, the reactions require 1 to 72 hours. The product can be isolated and purified by techniques well known in the art, such as extraction, evaporation, trituration, chromatography, and recrystallization.

20

In Reaction Scheme E, step 6, an appropriate acid of formula 21 undergoes an amidation reaction with an appropriate amine to give a compound of formula (1). An appropriate amine, NH_2R_5 , NHR_6R_7 , or NHR_8R_9 , is one which R_5 ,
25 R_6 and R_7 , and R_8 and R_9 are as desired in the final compound of formula (1).

An amidation reaction may proceed through the acid of formula 21 or the acid function of a compound of formula 21
30 may be first converted to an activated intermediate; such as an anhydride; a mixed anhydride of substituted phosphoric acid, such as dialkylphosphoric acid, diphenylphosphoric acid, halophosphoric acid; of aliphatic carboxylic acid, such as formic acid, acetic acid,
35 propionic acid, butyric acid, isobutyric acid, pivalic acid, 2-ethylbutyric acid, trichloroacetic acid, trifluoroacetic acid, and the like; of aromatic acids, such as benzoic acid and the like; or

ester, such as phenol ester, p-nitrophenol ester, 2,4-dinitrophenol ester, pentafluorophenol ester, pentachlorophenol ester, N-hydroxysuccinimide ester, N-hydroxyphthalimide ester, 1-hydroxy-1H-benzotriazole ester, and the like; activated amide, such as imidazole, dimethylpyrazole, triazole, or tetrazole; or the intermediate formed in the presence of coupling agents, such as dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide. Activated intermediates may be prepared and used directly, or are prepared and isolated before the addition of an appropriate amine, NH_2R_5 , NHR_6R_7 , or NHR_8R_9 . Alternately, activated intermediates may be prepared isolated and purified before the addition of an appropriate amine, NH_2R_5 , NHR_6R_7 , or NHR_8R_9 . The use and formation of activated intermediates is well known and appreciated in the art.

For example, an acid compound of formula 21 is contacted with a slight molar excess of an appropriate amine, NH_2R_5 , NHR_6R_7 , or NHR_8R_9 , or a salt of an appropriate amine and 1-hydroxybenzotriazole hydrate in the presence of a slight molar excess of a coupling agent, such as dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide. The reaction is carried out in the presence of a suitable base, such as diisopropylethyl amine, N-methylmorpholine, or triethylamine. If the salt of an amine is used an additional equimolar of a suitable base is added. The reaction is carried out in a suitable solvent, such as dichloromethane or chloroform. The product can be isolated and purified by techniques well known in the art, such as extraction, evaporation, chromatography, and recrystallization.

Alternatively, for example, an acid of formula 21 is contacted with 1.2 to 1.7 equivalents of a suitable base, such as N-methylmorpholine, in a suitable solvent, such as tetrahydrofuran. The reaction mixture is cooled to a

temperature of between -50°C and 0°C with -25°C to -20°C being preferred, before the addition of 1.2 to 1.7 equivalents of isobutyl chloroformate. The reaction is
5 allowed to stir for 30 minutes to 24 hours to allow for the formation of the mixed anhydride, an activated intermediate. While maintaining the temperature at between -50°C and 0°C an appropriate amine, NH_2R_5 , NHR_6R_7 , or NHR_8R_9 , is added, if the salt an appropriate amine is used an
10 additional equimolar amount of a suitable base is added. The reaction may, after the addition of amine is complete, be warmed to room temperature. Generally, the reaction requires from 2 to 48 hours. The product can be isolated and purified by techniques well known in the art, such as
15 extraction, evaporation, chromatography, and recrystallization.

The protected compounds of formula (1) prepared as described in Reaction Scheme E, optional step 4, step 5, and
20 step 6 can be deprotected as required as described in Reaction Scheme E, optional step 3.

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Reaction Scheme F

Reaction Scheme F is a general scheme for preparing
5 intermediates of formula 16 useful for preparing compounds
of formula (1).

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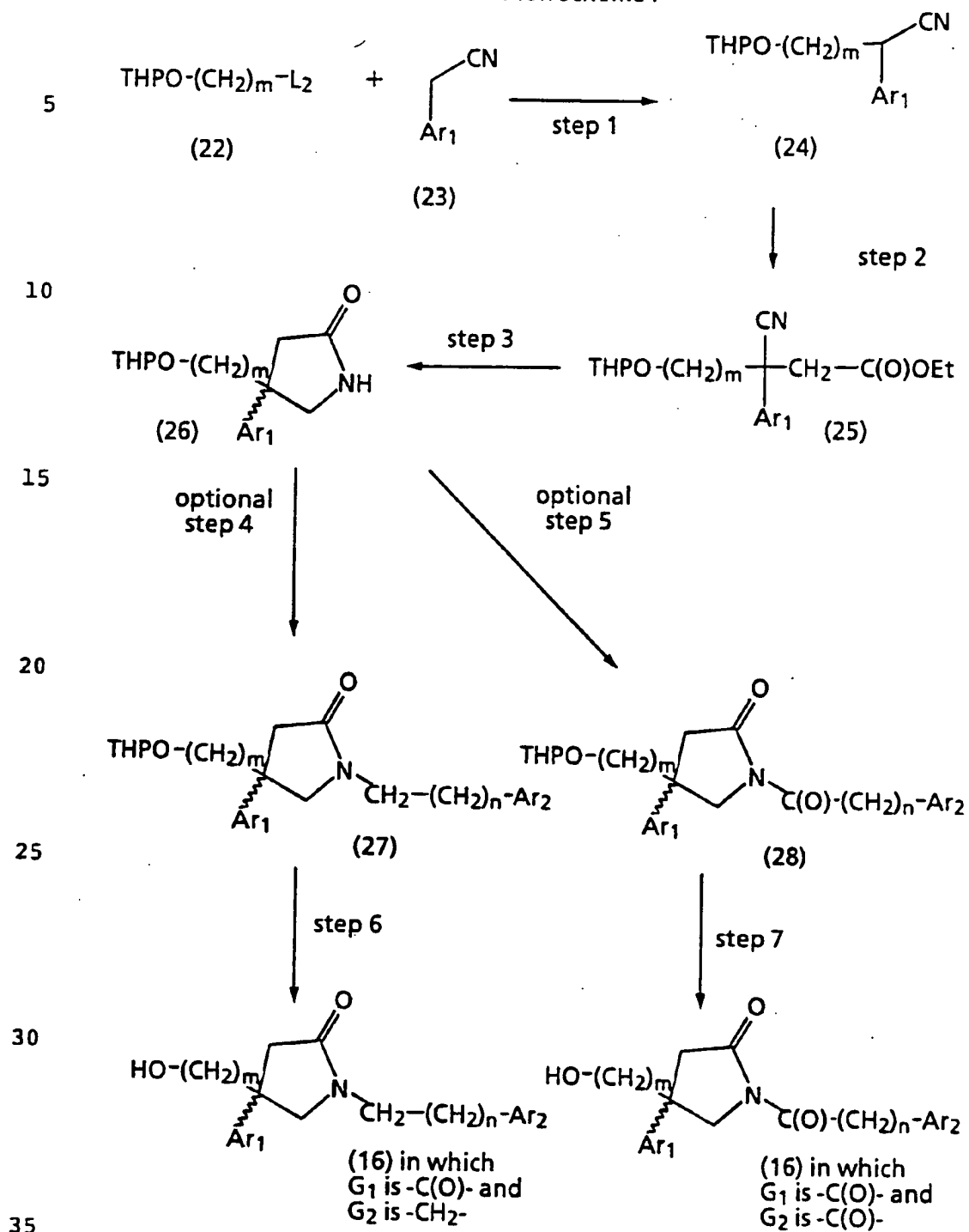
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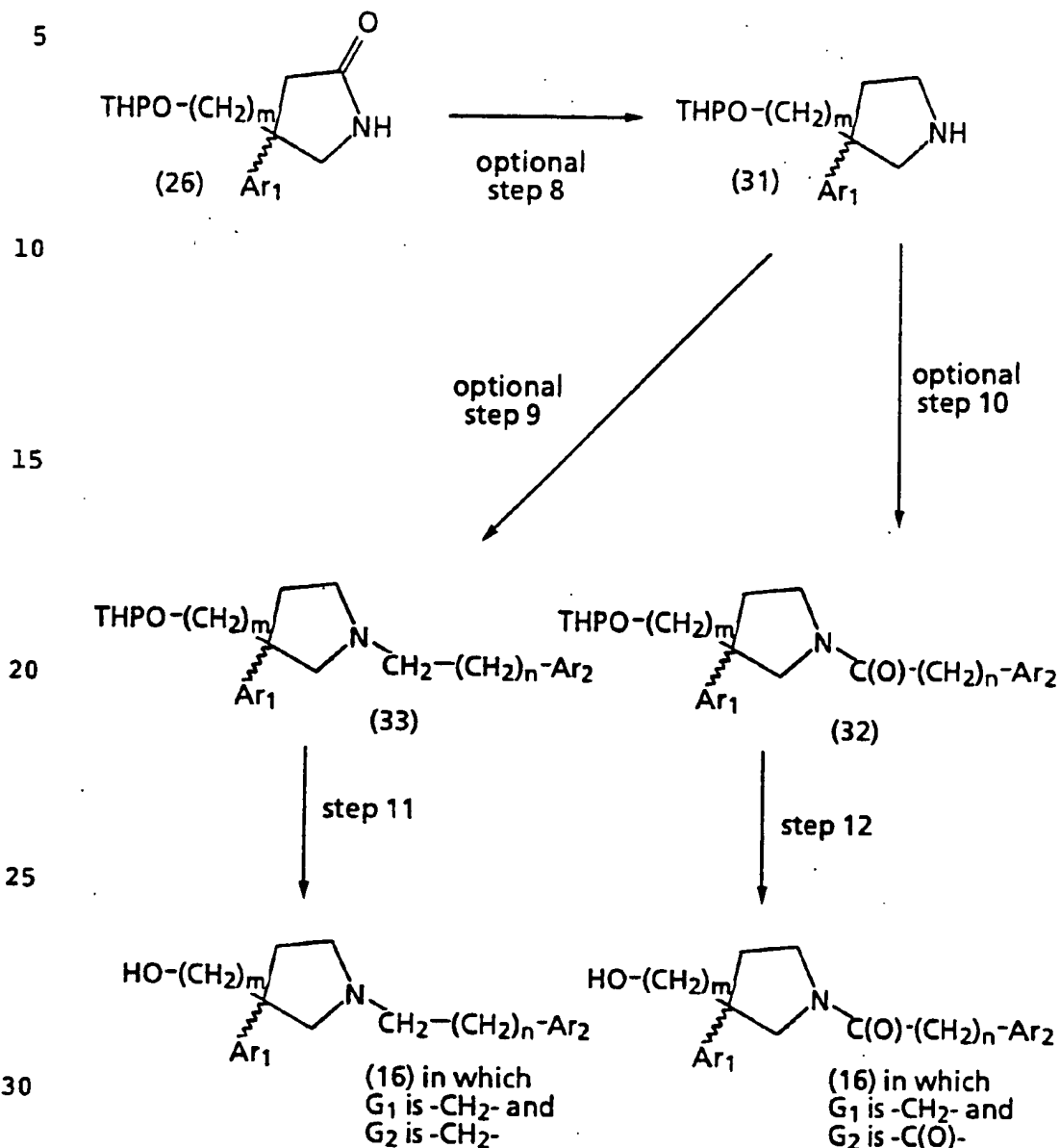
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Reaction Scheme F



In Reaction Scheme F, step 1, an appropriate aryl-acetonitrile of formula 23 is alkylated with an appropriate

Reaction Scheme F (Cont.)



ω-leaving group-THP-protected alcohol of formula 22 to give an ω-THP-protected-hydroxyalkyl-aryl-acetonitrile of formula 24. An appropriate aryl-acetonitrile of formula 23 is one in which Ar₁ is as desired in the final product of formula (1) or gives rise after deprotection to an Ar₁ as desired in the final product of formula (1). An appropriate ω-leaving group-THP-protected alcohol of

formula 22 in one in which m is 2 or 3 as desired in the final product of formula (1) and the leaving group, L₂, is one which can be displaced by an anion derived from an appropriate aryl-acetonitrile of formula 23. Suitable leaving groups include but are not limited to chloro, bromo, iodo, and mesylate with bromo being preferred.

For example, an appropriate aryl-acetonitrile of formula 23 is contacted with an equimolar amount of an appropriate ω -leaving group-THP-protected alcohol of formula 22. The reaction is carried out in the presence of a base, such as sodium hydride, sodium hexamethyldisilazide, potassium t-butoxide, and lithium diisopropylamide with sodium hydride and sodium hexamethyldisilazide being preferred. The reaction is carried out in a solvent, such as dimethylformamide or tetrahydrofuran. The reaction is generally carried out at temperatures of from -78°C to 0°C. Generally, the reactions require 1 to 72 hours. The product can be isolated and purified by techniques well known in the art, such as extraction, evaporation, trituration, chromatography, and recrystallization.

In Reaction Scheme F, step 2, an appropriate ω -THP-protected-hydroxyalkyl-aryl-acetonitrile of formula 24 is alkylated with ethyl bromoacetate to give a nitrile ester compound of formula 25.

For example, an appropriate ω -THP-protected-hydroxyalkyl-aryl-acetonitrile of formula 24 is contacted with approximately a molar equivalent of ethyl bromoacetate. The reaction is carried out in the presence a suitable base, such as, sodium hexamethyldisilazide or lithium diisopropylamide. The reaction is carried out in a suitable solvent, such as tetrahydrofuran. The reaction is generally carried out at temperatures of from -78°C to 0°C. Generally, the reactions require 1 to 72 hours. The

product can be isolated and purified by techniques well known in the art, such as extraction, evaporation, trituration, chromatography, and recrystallization.

5

In Reaction Scheme F, step 3, an appropriate nitrile ester compound of formula 25 is reduced and cyclized to give a 5-oxo-3-aryl-3-(ω -THP-protected-hydroxyalkyl) pyrrolidine of formula 26.

10

For example, an appropriate nitrile ester compound of formula 25 is contacted with an appropriate reducing agent, such as sodium borohydride in the presence of cobalt (II) chloride hexahydrate or hydrogen in the presence of a suitable catalyst, such as Raney nickel. For compounds of formula 25 in which Ar₁ is thienyl, sodium borohydride in the presence of cobalt (II) chloride hexahydrate is preferred.

When sodium borohydride in the presence of cobalt chloride is used, the reaction is carried out in a suitable solvent, such as methanol, or ethanol. The reaction is generally carried out at temperatures of from 0°C to 50°C.. Generally, the reactions require 1 to 72 hours. The product can be isolated and purified by techniques well known in the art, such as extraction with aqueous acid, evaporation, trituration, chromatography, and recrystallization.

When Raney nickel is used, the reaction is carried out in a suitable solvent containing ammonia, such as ethanol/ammonium hydroxide. The reaction is generally carried out at temperatures of from ambient temperature to 50°C.. The reaction is carried out at pressures of from 15 psi to 120 psi in an apparatus designed for carrying out reactions under pressure, such as a Parr hydrogenation apparatus. The product can be isolated by carefully removing the catalyst by filtration and evaporation. The

product can be purified by extraction, evaporation, trituration, chromatography, and recrystallization.

- 5 In Reaction Scheme F, optional step 4, an appropriate 5-oxo-3-aryl-3-(ω -THP-protected-hydroxyalkyl) pyrrolidine of formula 26 is alkylated with an appropriate alkyl halide, $X-CH_2-(CH_2)_n-Ar_2$, to an N-arylaklyl-5-oxo-3-aryl-3-(ω -THP-protected-hydroxyalkyl) pyrrolidine of formula 27.
- 10 An appropriate alkyl halide, $X-CH_2-(CH_2)_n-Ar_2$, is one in which X is chloro, bromo, or iodo; n is as desired in the final product of formula (1), and Ar_2 is as desired in formula (1).
- 15 For example, an appropriate 5-oxo-3-aryl-3-(ω -THP-protected-hydroxyalkyl) pyrrolidine of formula 26 is contacted with from 1 to 5 molar equivalents of an appropriate alkyl halide, $X-CH_2-(CH_2)_n-Ar_2$. The reaction is carried out in a suitable solvent, such as tetrahydrofuran,
- 20 dimethyl sulfoxide, or dimethylformamide. The reaction is carried out in the presence of a base, such as sodium hydride, potassium t-butoxide, or lithium diisopropylamide with sodium hydride being preferred. The reaction is generally carried out at temperatures of from 0°C to 50°C.
- 25 Generally, the reactions require 1 to 72 hours. The product can be isolated and purified by techniques well known in the art, such as extraction, evaporation, trituration, chromatography, and recrystallization.
- 30 In Reaction Scheme F, optional step 5, an appropriate 5-oxo-3-aryl-3-(ω -THP-protected-hydroxyalkyl) pyrrolidine of formula 26 is aroylated with an appropriate aroyl halide, aryl anhydride, or aryl mixed anhydride, $A-C(O)-(CH_2)_n-Ar_2$, to an N-aroyl-5-oxo-3-aryl-3-(ω -THP-protected-
- 35 hydroxyalkyl) pyrrolidine of formula 28. An appropriate aroyl halide, aryl anhydride, or aryl mixed anhydride, $A-C(O)-(CH_2)_n-Ar_2$, is one in which A is an activated leaving group, such as chloro or bromo, an anhydride, or mixed

anhydride, n is as desired in the final product of formula (1), and Ar₂ is as desired in formula (1).

5 For example, an appropriate 5-oxo-3-aryl-3-(ω-THP-protected-hydroxyalkyl) pyrrolidine of formula 26 is contacted with 1 to 1.5 molar equivalents of an appropriate
10 aroyl halide, aryl anhydride, or aryl mixed anhydride, A-C(O)-(CH₂)_n-Ar₂. The reaction is carried out in a suitable solvent, such as tetrahydrofuran, N,N-dimethylaniline, or diethyl ether. The reaction is carried out in the presence of a base, such as sodium hydride, N,N-dimethylaniline, potassium t-butoxide, or lithium diisopropylamide with sodium hydride being preferred. The reaction is generally
15 carried out at temperatures of from -20°C to the reflux temperature of the solvent. Generally, the reactions require 1 to 24 hours. The product can be isolated and purified by techniques well known in the art, such as extraction, evaporation, trituration, chromatography, and
20 recrystallization.

In Reaction Scheme F, step 6, an N-arylaklyl-5-oxo-3-aryl-3-(ω-THP-protected-hydroxyalkyl) pyrrolidine of formula 27 is deprotected to give an N-arylaklyl-5-oxo-3-
25 aryl-3-(ω-hydroxyalkyl) pyrrolidine of formula 16 which gives rise to compounds of formula (1) in which G₁ is -C(O)- and G₂ is -CH₂- and m, n, Ar₁, and Ar₂ are as desired in the final product of formula (1) or give rise after deprotection to Ar₁ as desired in the final product of
30 formula (1).

For example, an N-arylaklyl-5-oxo-3-aryl-3-(ω-THP-protected-hydroxyalkyl) pyrrolidine of formula 27 is treated with a suitable acid, such as p-toluenesulfonic
35 acid. The reaction is carried out in a suitable solvent, such as methanol or ethanol. The product is isolated by evaporation and purified by techniques well known in the

art, such as extraction, evaporation, trituration, chromatography, and recrystallization.

5 In Reaction Scheme F, step 7, an N-aryl-5-oxo-3-aryl-3-(ω -THP-protected-hydroxyalkyl) pyrrolidine of formula 28 is deprotected, as taught above for Reaction Scheme F, step 6, to give an N-aryl-5-oxo-3-aryl-3-(ω -hydroxyalkyl) pyrrolidine of formula 16 of which gives rise to compounds
10 of formula (1) in which G_1 is $-C(O)-$ and G_2 is $-C(O)-$ and m, n, Ar_1 , and Ar_2 are as desired in the final product of formula (1) or give rise after deprotection to Ar_1 as desired in the final product of formula (1).

15 In Reaction Scheme F, optional step 8, an appropriate 5-oxo-3-aryl-3-(ω -THP-protected-hydroxyalkyl) pyrrolidine of formula 26 is reduced to give a 3-aryl-3-(ω -THP-protected-hydroxyalkyl) pyrrolidine of formula 31.

20 For example, an appropriate 5-oxo-3-aryl-3-(ω -THP-protected-hydroxyalkyl) pyrrolidine of formula 26 is contacted with a suitable reducing agent, such as lithium aluminum hydride, aluminum hydride, or borane dimethyl sulfide complex. The reaction is carried out in a suitable
25 solvent, such as tetrahydrofuran. The reaction is generally carried out at temperature of from 0°C to the refluxing temperature of the solvent. Generally, the reactions require 1 to 72 hours. The product can be isolated and purified by techniques well known in the art,
30 such as quenching of borane or aluminum complexes, extraction, evaporation, trituration, chromatography, and recrystallization.

In Reaction Scheme F, optional step 9, an appropriate
35 3-aryl-3-(ω -THP-protected-hydroxyalkyl) pyrrolidine of formula 31 is alkylated with an appropriate alkyl halide, $X-CH_2-(CH_2)_n-Ar_2$, to an N-arylaklyl-3-aryl-3-(ω -THP-protected-hydroxyalkyl) pyrrolidine of formula 33. An

appropriate alkyl halide, $X-CH_2-(CH_2)_n-Ar_2$, is one in which X is chloro or bromo, n is as desired in the final product of formula (1), and Ar_2 is as desired in formula (1).

5

For example, an appropriate 3-aryl-3-(ω -THP-protected-hydroxyalkyl) pyrrolidine of formula 31 is contacted with from 1.0 to 1.2. molar equivalents of an appropriate alkyl halide, $X-CH_2-(CH_2)_n-Ar_2$. The reaction is carried out in a
10 suitable solvent, such as tetrahydrofuran, dimethyl sulfoxide, acetonitrile, tetrahydrofuran/ water, toluene, toluene/ water, or dimethylformamide. The reaction is carried out in the presence of a base, such as sodium carbonate, sodium bicarbonate, potassium carbonate,
15 triethylamine diisopropylethylamine, or pyridine. The reaction is generally carried out at temperatures of from 0°C to reflux temperature of solvent. Generally, the reactions require 1 to 72 hours. The product can be isolated and purified by techniques well known in the art,
20 such as extraction, evaporation, trituration, chromatography, and recrystallization.

In Reaction Scheme F, optional step 10, an appropriate 3-aryl-3-(ω -THP-protected-hydroxyalkyl) pyrrolidine of
25 formula 31 is aroylated with an appropriate aroyl halide, aryl anhydride, or aryl mixed anhydride, $A-C(O)-(CH_2)_n-Ar_2$, to an N-aroyl-3-aryl-3-(ω -THP-protected-hydroxyalkyl) pyrrolidine of formula 32. An appropriate aroyl halide, aryl anhydride, or aryl mixed anhydride, $A-C(O)-(CH_2)_n-Ar_2$,
30 is one in which A is an activated leaving group, such as chloro or bromo, an anhydride, or mixed anhydride, n is as desired in the final product of formula (1), and Ar_2 is as desired in formula (1).

35 For example, an appropriate 3-aryl-3-(ω -THP-protected-hydroxyalkyl) pyrrolidine of formula 31 is contacted with 1 to 1.5 molar equivalents of an appropriate aroyl halide, aryl anhydride, or aryl mixed anhydride, $A-C(O)-(CH_2)_n-Ar_2$.

The reaction is carried out in a suitable solvent, such as tetrahydrofuran, acetonitrile, dimethylformamide, or pyridine. The reaction is carried out in the presence of a base, such as sodium carbonate, sodium bicarbonate, triethylamine, diisopropylethylamine, or pyridine. The reaction is generally carried out at temperatures of from -20°C to 50°C. Generally, the reactions require 1 to 24 hours. The product can be isolated and purified by techniques well known in the art, such as extraction, evaporation, trituration, chromatography, and recrystallization.

In Reaction Scheme F, step 11, an N-arylaklyl-3-aryl-3-(ω -THP-protected-hydroxyalkyl) pyrrolidine of formula 33 is deprotected to give an N-arylaklyl-3-aryl-3-(ω -hydroxyalkyl) pyrrolidine of formula 16 which gives rise to compounds of formula (1) in which G_1 is $-\text{CH}_2-$, G_2 is $-\text{CH}_2-$, m , n , Ar_1 , and Ar_2 are as desired in the final product of formula (1) or give rise after deprotection to Ar_1 as desired in the final product of formula (1).

For example, an N-arylaklyl-3-aryl-3-(ω -THP-protected-hydroxyalkyl) pyrrolidine of formula 33 is treated with a suitable acid, such as p-toluenesulfonic acid. The reaction is carried out in a suitable solvent, such as methanol or ethanol. The product is isolated by evaporation and purified by techniques well known in the art, such as extraction, evaporation, trituration, chromatography, and recrystallization.

In Reaction Scheme F, step 12, an N-aroyle-3-aryl-3-(ω -THP-protected-hydroxyalkyl) pyrrolidine of formula 32 is deprotected, as taught above in Reaction Scheme F, step 11, to give an N-aroyle-3-aryl-3-(ω -hydroxyalkyl) pyrrolidine of formula 16 which gives rise to compounds of formula (1) in which G_1 is $-\text{CH}_2-$, G_2 is $-\text{C}(\text{O})-$, and m , n , Ar_1 , and Ar_2 are as desired in the final product of formula (1) or give

rise after deprotection to Ar₁ as desired in the final product of formula (1).

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Reaction Scheme G

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Reaction Scheme G is a general scheme for preparing intermediates giving rise to compounds of formula (1) wherein m is 2.

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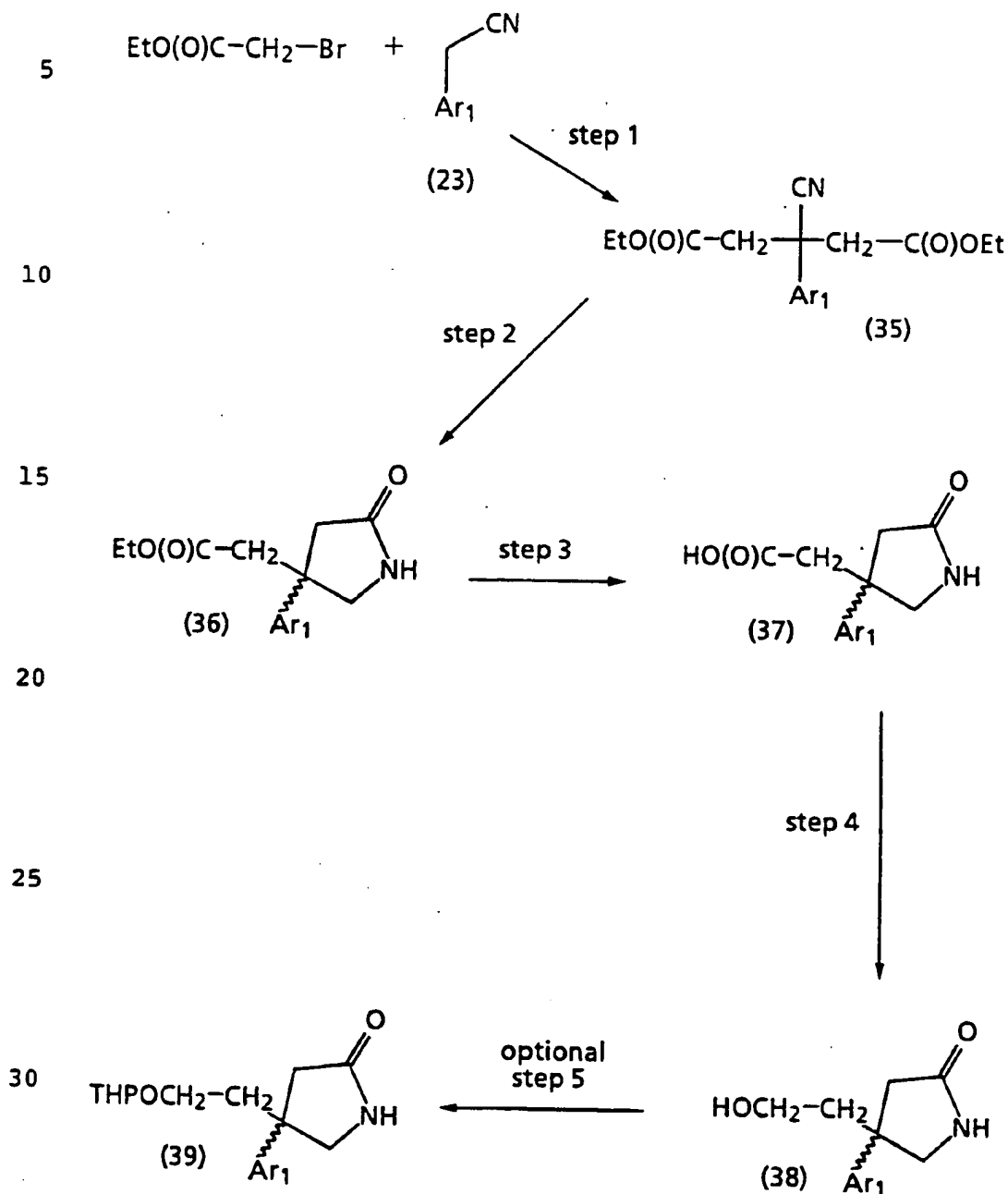
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Reaction Scheme G



35 In Reaction Scheme G, step 1, an appropriate aryl acetonitrile of formula 23 is alkylated twice with ethyl bromoacetate to give a nitrile bis-ester compound of formula 35. An appropriate aryl acetonitrile of formula 23 is one in which Ar_1 is as is desired in the final product of

formula (1) or gives rise after deprotection to an Ar₁ as desired in the final product of formula (1).

5 For example, an appropriate aryl acetonitrile of formula 23 is contacted with 2.0 to 3.0 molar equivalents of ethyl bromoacetate. The reaction is carried out in the presence of approximately 2.0 to 3.0 molar equivalents of a
10 suitable base, such as sodium hexamethyldisilazide or lithium diisopropylamide. The reaction is carried out in a suitable solvent, such as tetrahydrofuran. The reaction is generally carried out at temperatures of from - 78°C to 0°C. Generally, the reactions require 1 to 72 hours. The product can be isolated and purified by techniques well
15 known in the art, such as extraction, evaporation, trituration, chromatography, and recrystallization.

 In Reaction Scheme G, step 2, an appropriate nitrile bis-ester compound of formula 35 is reduced and cyclized to
20 give a 5-oxo-3-aryl-3-acetic acid ester pyrrolidine of formula 36.

 For example, an appropriate nitrile bis-ester compound of formula 35 is contacted with an appropriate reducing
25 agent, such as sodium borohydride in the presence of cobalt II chloride hexahydrate or hydrogen in the presence of a suitable catalyst, such as Raney nickel. For compounds of formula 35 in which Ar₁ is thienyl, sodium borohydride in the presence of cobalt II chloride hexahydrate is
30 preferred.

 When sodium borohydride in the presence of cobalt chloride is used, the reaction is carried out in a suitable solvent, such as methanol, or ethanol. The reaction is
35 generally carried out at temperatures of from 0°C to 50°C.. Generally, the reactions require 1 to 72 hours. The product can be isolated and purified by techniques well known in the art, such as extraction with aqueous acid,

evaporation, trituration, chromatography, and recrystallization.

5 When Raney nickel is used, the reaction is carried out in a suitable solvent containing ammonia, such as ethanol/ammonium hydroxide. The reaction is generally carried out at temperatures of from ambient temperature to 50°C.. The reaction is carried out at pressures of from 15
10 psi to 120 psi in an apparatus designed for carrying out reactions under pressure, such as a Parr hydrogenation apparatus. The product can be isolated by carefully removing the catalyst by filtration and evaporation. The product can be purified by extraction, evaporation,
15 trituration, chromatography, and recrystallization.

 In Reaction Scheme G, step 3, an appropriate 5-oxo-3-aryl-3-acetic acid ester pyrrolidine of formula 36 is hydrolyzed to give a 5-oxo-3-aryl-3-acetic acid pyrrolidine
20 of formula 37.

 For example, an appropriate 5-oxo-3-aryl-3-acetic acid ester pyrrolidine of formula 36 is contacted with a suitable hydrolyzing agent, such as sodium hydroxide,
25 potassium hydroxide, or lithium hydroxide. The reaction is carried out in a suitable solvent such as water, tetrahydrofuran/water mixtures, methanol, methanol/water mixtures, or ethanol/water mixtures. The reaction is generally carried out at temperatures of from 0°C to the
30 refluxing temperature of the solvent. Generally, the reactions require 1 to 72 hours. The product can be isolated and purified by techniques well known in the art, such as extraction, evaporation, trituration, chromatography, and recrystallization.

35

 In Reaction Scheme G, step 4, an appropriate 5-oxo-3-aryl-3-acetic acid pyrrolidine of formula 37 is reduced to

give a 5-oxo-3-aryl-3-(2-hydroxyethyl) pyrrolidine of formula 38.

5 For example, an appropriate 5-oxo-3-aryl-3-acetic acid pyrrolidine of formula 37 is contacted with a suitable borane reagent, such as borane dimethyl sulfide complex or sodium borohydride reduction of a mixed anhydride intermediate formed by methods well known in the art. The
10 reaction is carried out in a suitable solvent, such as tetrahydrofuran. The reaction is generally carried out at a temperature of from 0°C to the refluxing temperature of the solvent. When complete the reaction is quenched by the careful addition of a suitable aqueous acid solution, such
15 as 1 M hydrochloric acid solution. The product can be isolated and purified by techniques well known in the art, such as extraction, evaporation, trituration, chromatography, and recrystallization.

20 In Reaction Scheme G, step 5, an appropriate 5-oxo-3-aryl-3-(2-hydroxyethyl) pyrrolidine of formula 38 is protected using dihydropyran to give a 5-oxo-3-aryl-3-(2-THP-protected-hydroxyethyl) pyrrolidine of formula 39.

25 For example, an appropriate 5-oxo-3-aryl-3-(2-hydroxyethyl) pyrrolidine of formula 38 is contacted with dihydropyran. The reaction is carried out in the presence of a catalytic amount of a suitable acid, such as p-toluenesulfonic acid, pyridinium p-toluenesulfonic acid, or
30 a sulfonic acid containing resin, such as Amberlyst H-15. The reaction is carried out in a suitable solvent, such as dichloromethane. The reaction is generally carried out at ambient temperature. The product can be isolated and purified by techniques well known in the art, such as
35 extraction, evaporation, trituration, chromatography, and recrystallization.

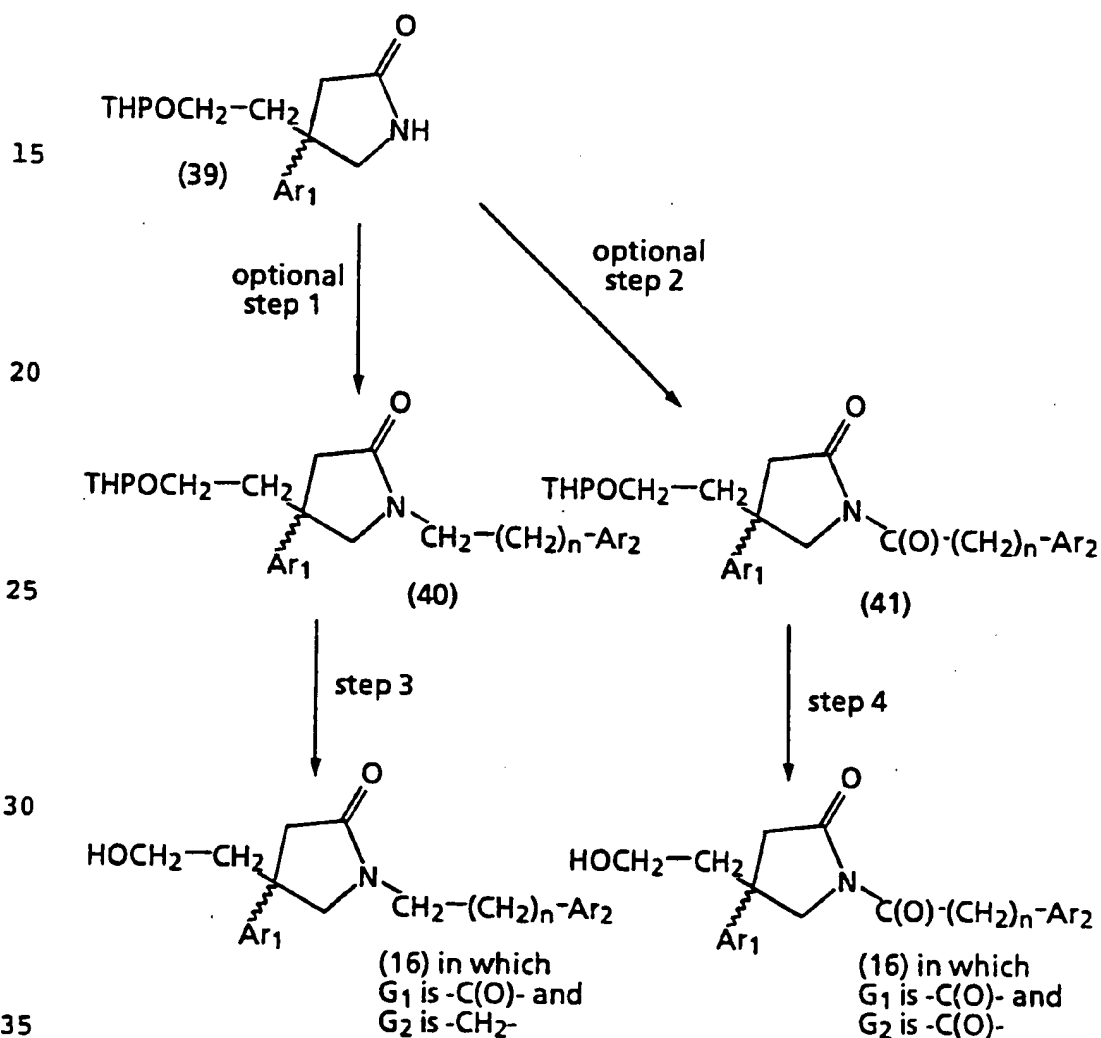
Reaction Scheme H

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Reaction Scheme H is a general Scheme H for preparing intermediates for preparing compounds of formula (1) wherein m is 2 and G_1 is $-C(O)-$.

10

Reaction Scheme H



In Reaction Scheme H, optional step 1, an appropriate 5-oxo-3-aryl-3-(ω -THP-protected-hydroxyethyl) pyrrolidine

of formula 39 is alkylated with an appropriate alkyl halide, $X-CH_2-(CH_2)_n-Ar_2$, to an N-arylalkyl-5-oxo-3-aryl-3-(ω -THP-protected-hydroxyethyl) pyrrolidine of formula 40.

- 5 An appropriate alkyl halide, $X-CH_2-(CH_2)_n-Ar_2$, is one in which X is chloro, bromo, or iodo; n is as desired in the final product of formula (1), and Ar_2 is as desired in formula (1).

- 10 For example, an appropriate 5-oxo-3-aryl-3-(ω -THP-protected-hydroxyethyl) pyrrolidine of formula 39 is contacted with from 1 to 5 molar equivalents of an appropriate alkyl halide, $X-CH_2-(CH_2)_n-Ar_2$. The reaction is carried out in a suitable solvent, such as tetrahydrofuran,
15 dimethyl sulfoxide, or dimethylformamide. The reaction is carried out in the presence of a base, such as sodium hydride, sodium hexamethyldisilazide, potassium t-butoxide, or lithium diisopropylamide with sodium hydride being preferred. The reaction is generally carried out at
20 temperatures of from 0°C to the refluxing temperature of the solvent. Generally, the reactions require 1 to 72 hours. The product can be isolated and purified by techniques well known in the art, such as extraction, evaporation, trituration, chromatography, and
25 recrystallization.

- In Reaction Scheme H, optional step 2, an appropriate 5-oxo-3-aryl-3-(ω -THP-protected-hydroxyethyl) pyrrolidine of formula 39 is aroylated with an appropriate aroyl
30 halide, aryl anhydride, or aryl mixed anhydride, $A-C(O)-(CH_2)_n-Ar_2$, to an N-aroyl-5-oxo-3-aryl-3-(ω -THP-protected-hydroxyethyl) pyrrolidine of formula 41. An appropriate aroyl halide, aryl anhydride, or aryl mixed anhydride, $A-C(O)-(CH_2)_n-Ar_2$, is one in which A is an activated leaving
35 group, such as chloro or bromo, an anhydride, or mixed anhydride, n is as desired in the final product of formula (1), and Ar_2 is as desired in formula (1).

For example, an appropriate 5-oxo-3-aryl-3-(ω -THP-protected-hydroxyethyl) pyrrolidine of formula 39 is contacted with 1 to 1.5 molar equivalents of an appropriate aroyl halide, aryl anhydride, or aryl mixed anhydride, A-C(O)-(CH₂)_n-Ar₂. The reaction is carried out in a suitable solvent, such as tetrahydrofuran, N,N-dimethylaniline, or diethyl ether. The reaction is carried out in the presence of a base, such as sodium hydride, N,N-dimethylaniline, potassium t-butoxide, or lithium diisopropylamide with sodium hydride being preferred. The reaction is generally carried out at temperatures of from -20°C to 50°C. Generally, the reactions require 1 to 24 hours. The product can be isolated and purified by techniques well known in the art, such as extraction, evaporation, trituration, chromatography, and recrystallization.

In Reaction Scheme H, step 3, an N-arylalkyl-5-oxo-3-aryl-3-(ω -THP-protected-hydroxyethyl) pyrrolidine of formula 40 is deprotected to give an N-arylalkyl-5-oxo-3-aryl-3-(ω -hydroxyethyl) pyrrolidine of formula 16 which gives rise to compounds of formula (1) in which G₁ is -C(O)-, G₂ is -CH₂-, m is 2, and n, Ar₁, and Ar₂ are as desired in the final product of formula (1) or give rise after deprotection to Ar₁ as desired in the final product of formula (1).

For example, an N-arylalkyl-5-oxo-3-aryl-3-(ω -THP-protected-hydroxyethyl) pyrrolidine of formula 40 is treated with a suitable acid, such as p-toluenesulfonic acid. The reaction is carried out in a suitable solvent, such as methanol or ethanol. The product is isolated by evaporation and purified by techniques well known in the art, such as extraction, evaporation, trituration, chromatography, and recrystallization.

In Reaction Scheme H, step 4, an N-aroyle-5-oxo-3-aryl-3-(ω -THP-protected-hydroxyethyl) pyrrolidine of formula 41

is deprotected, as taught above, to give an an N-aroyle-5-oxo-3-aryl-3-(ω -hydroxyalkyl) pyrrolidine of formula 16 which gives rise to compounds of formula (1) in which G_1 is

5 -C(O)-, G_2 is -C(O)-, m is 2, and n , Ar_1 , and Ar_2 are as desired in the final product of formula (1) or give rise after deprotection to Ar_1 as desired in the final product of formula (1).

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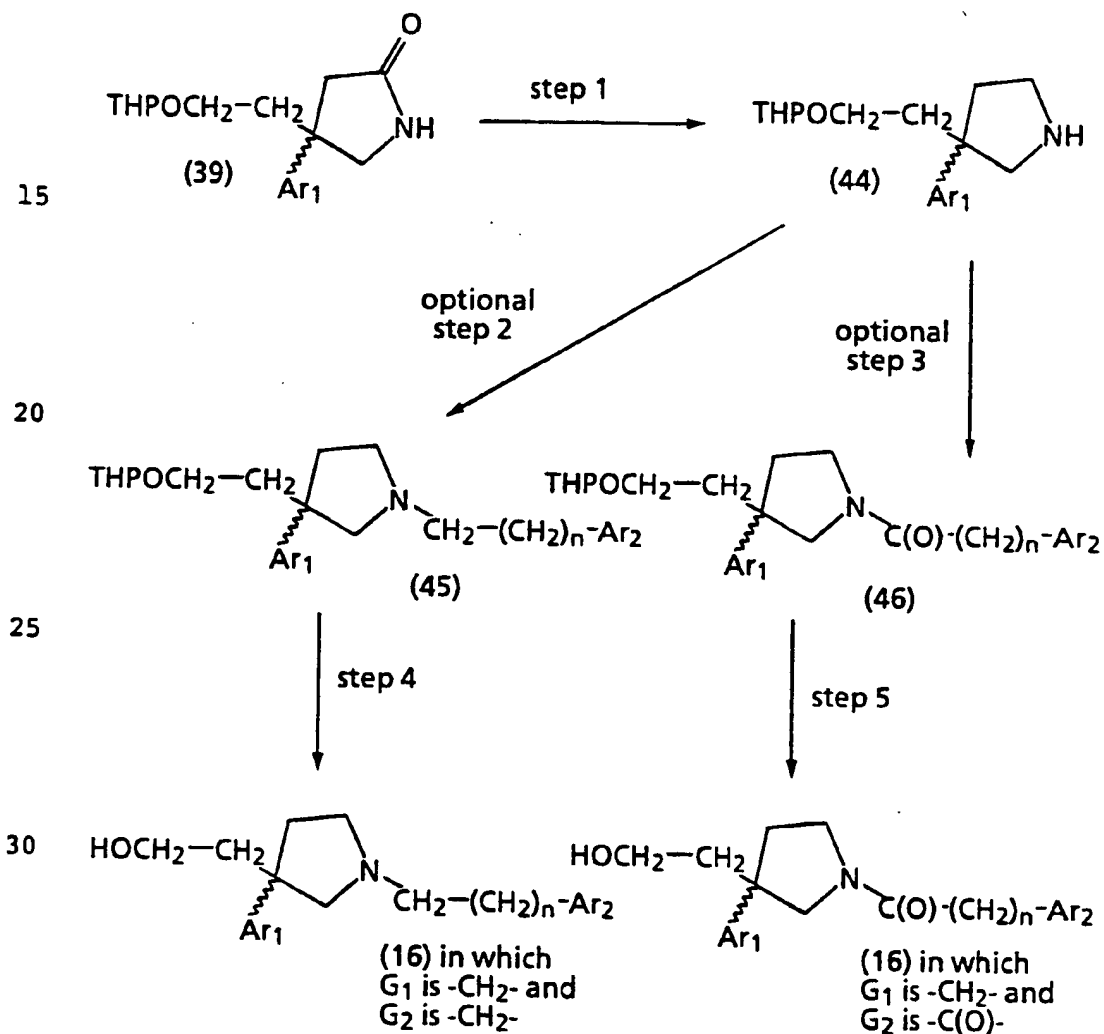
Reaction Scheme I

5

Reaction Scheme I is a general scheme for preparing intermediates for preparing compounds of formula (1) wherein m is 2 and G_1 is $-\text{CH}_2-$.

Reaction Scheme I

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In Reaction Scheme I, step 1, an appropriate 5-oxo-3-aryl-3-(ω-THP-protected-hydroxyethyl)-pyrrolidine of formula 39 is reduced to give a 3-aryl-3-(ω-THP-protected-hydroxyethyl) pyrrolidine of formula 44.

For example, an appropriate 5-oxo-3-aryl-3-(ω -THP-protected-hydroxyethyl) pyrrolidine of formula 39 is
5 contacted with a suitable reducing agent, such as lithium aluminum hydride, aluminum hydride, or borane dimethyl sulfide complex. The reaction is carried out in a suitable solvent, such as tetrahydrofuran. The reaction is
10 generally carried out at temperature of from 0°C to the refluxing temperature of the solvent. Generally, the reactions require 1 to 72 hours. The product can be isolated and purified by techniques well known in the art, such as quench of borane or aluminum complexes, extraction, evaporation, trituration, chromatography, and
15 recrystallization.

In Reaction Scheme I, optional step 2, an appropriate 3-aryl-3-(ω -THP-protected-hydroxyethyl)-pyrrolidine of formula 44 is alkylated with an appropriate alkyl halide,
20 $X-CH_2-(CH_2)_n-Ar_2$, to an N-arylalkyl-3-aryl-3-(ω -THP-protected-hydroxyethyl)-pyrrolidine of formula 45. An appropriate alkyl halide, $X-CH_2-(CH_2)_n-Ar_2$, is one in which X is chloro, bromo, or iodo; n is as desired in the final product of formula (1), and Ar_2 is as desired in formula
25 (1).

For example, an appropriate 3-aryl-3-(ω -THP-protected-hydroxyethyl) pyrrolidine of formula 45 is contacted with
30 from 1.0 to 1.2 molar equivalents of an appropriate alkyl halide, $X-CH_2-(CH_2)_n-Ar_2$. The reaction is carried out in a suitable solvent, such as tetrahydrofuran, dimethyl sulfoxide, acetonitrile, tetrahydrofuran, toluene, tetrahydrofuran/water mixtures, toluene/water mixtures, or dimethylformamide. The reaction is carried out in the
35 presence of a base, such as sodium carbonate, potassium carbonate, sodium bicarbonate, triethylamine diisopropylethylamine, or pyridine. The reaction is generally carried out at temperatures of from 0°C to the

refluxing temperature of the solvent. Generally, the reactions require 1 to 72 hours. The product can be isolated and purified by techniques well known in the art, such as extraction, evaporation, trituration, chromatography, and recrystallization.

In Reaction Scheme I, optional step 3, an appropriate 3-aryl-3-(ω -THP-protected-hydroxyethyl) pyrrolidine of formula 44 is aroylated with an appropriate aroyl halide, aryl anhydride, or aryl mixed anhydride, $A-C(O)-(CH_2)_n-Ar_2$, to an N-aroyl-3-aryl-3-(ω -THP-protected-hydroxyethyl) pyrrolidine of formula 46. An appropriate aroyl halide, aryl anhydride, or aryl mixed anhydride, $A-C(O)-(CH_2)_n-Ar_2$, is one in which A is an activated leaving group, such as chloro or bromo, an anhydride, or mixed anhydride, n is as desired in the final product of formula (1), and Ar_2 is as desired in formula (1).

For example, an appropriate 3-aryl-3-(ω -THP-protected-hydroxyethyl) pyrrolidine of formula 44 is contacted with 1 to 1.5 molar equivalents of an appropriate aroyl halide, aryl anhydride, or aryl mixed anhydride, $A-C(O)-(CH_2)_n-Ar_2$. The reaction is carried out in a suitable solvent, such as tetrahydrofuran, dichloromethane, acetonitrile, dimethylformamide, or pyridine. The reaction is carried out in the presence of a base, such as sodium carbonate, potassium carbonate, sodium bicarbonate, triethylamine diisopropylethylamine, or pyridine. The reaction is generally carried out at temperatures of from -20°C to 50°C . Generally, the reactions require 1 to 24 hours. The product can be isolated and purified by techniques well known in the art, such as extraction, evaporation, trituration, chromatography, and recrystallization.

In Reaction Scheme I, step 4, an N-arylalkyl-3-aryl-3-(ω -THP-protected-hydroxyethyl) pyrrolidine of formula 45 is deprotected to give an N-arylalkyl-3-aryl-3-(ω -

hydroxyethyl) pyrrolidine of formula 16 which gives rise to compounds of formula (1) in which G_1 is $-CH_2-$, G_2 is $-CH_2-$, m is 2, n , Ar_1 , and Ar_2 are as desired in the final product of formula (1) or give rise after deprotection to Ar_1 as desired in the final product of formula (1).

For example, an N-arylalkyl-3-aryl-3-(ω -THP-protected-hydroxyethyl) pyrrolidine of formula 16 is treated with a suitable acid, such as p-toluenesulfonic acid. The reaction is carried out in a suitable solvent, such as methanol or ethanol. The product is isolated by evaporation and purified by techniques well known in the art, such as extraction, evaporation, trituration, chromatography, and recrystallization.

In Reaction Scheme I, step 4, an N-aroyle-3-aryl-3-(ω -THP-protected-hydroxyethyl) pyrrolidine of formula 46 is deprotected, as taught above, to give an N-aroyle-3-aryl-3-(ω -hydroxyethyl) pyrrolidine of formula 16 which gives rise to compounds of formula (1) in which G_1 is $-CH_2-$, G_2 is $-C(O)-$, and m is 2, n , Ar_1 , and Ar_2 are as desired in the final product of formula (1) or give rise after deprotection to Ar_1 as desired in the final product of formula (1).

30

35

Reaction Scheme J

Reaction Scheme J is an alternate scheme for preparing
5 some intermediates giving rise to compounds of formula (1)
wherein m is 2 and G₁ is -CH₂- and G₂ is -C(O)- and for
preparing some intermediates giving rise to compounds of
formula (1) wherein m is 2 and G₁ is -C(O)- and G₂ is -CH₂-.

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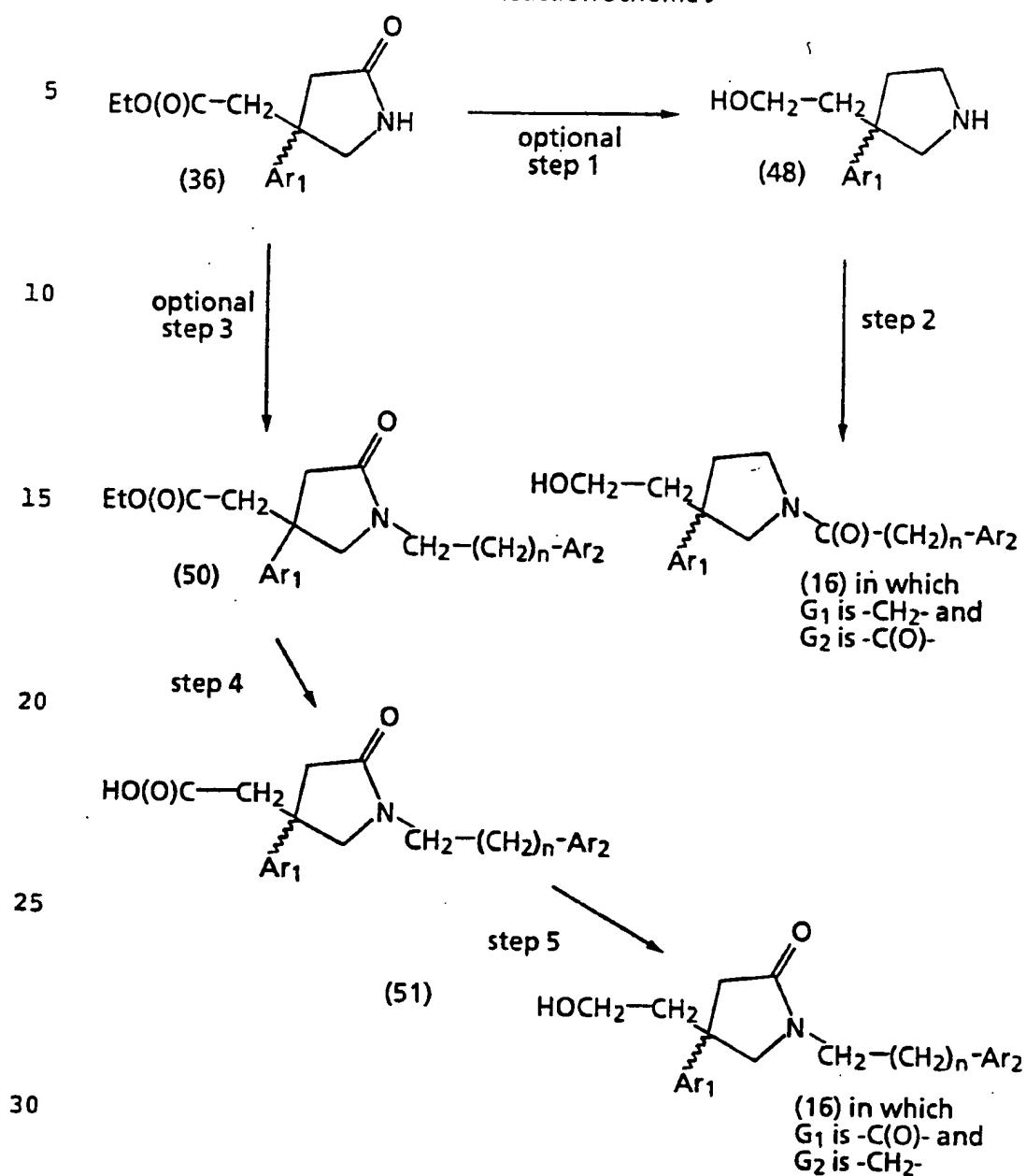
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Reaction Scheme J



In Reaction Scheme J, optional step 1, an appropriate
 5-oxo-3-aryl-3-acetic acid ester pyrrolidine of formula 36
 35 is reduced to give a 3-aryl-3-(ω-hydroxyethyl) pyrrolidine
 of formula 48.

For example, an appropriate 5-oxo-3-aryl-3-acetic acid ester pyrrolidine of formula 36 is contacted with a suitable reducing agent, such as lithium aluminum hydride, aluminum hydride, or borane dimethyl sulfide complex. The reaction is carried out in a suitable solvent, such as tetrahydrofuran. The reaction is generally carried out at temperature of from 0°C to the refluxing temperature of the solvent. Generally, the reactions require 1 to 72 hours. The product can be isolated and purified by techniques well known in the art, such as extraction, evaporation, trituration, chromatography, and recrystallization.

In Reaction Scheme J, step 2, an appropriate 3-aryl-3-(ω-hydroxyethyl)-pyrrolidine of formula 48 is aroylated with an appropriate aroyl halide, aryl anhydride, or aryl mixed anhydride, $A-C(O)-(CH_2)_n-Ar_2$, to an N-aroyl-3-aryl-3-(ω-hydroxyethyl)-pyrrolidine of formula 16. An appropriate aroyl halide, aryl anhydride, or aryl mixed anhydride, $A-C(O)-(CH_2)_n-Ar_2$, is one in which A is an activated leaving group, such as chloro, bromo, or iodo; an anhydride, or mixed anhydride, n is as desired in the final product of formula (1), and Ar_2 is as desired in formula (1).

For example, an appropriate 3-aryl-3-(ω-hydroxyethyl) pyrrolidine of formula 48 is contacted with 1 to 1.1 molar equivalents of an appropriate aroyl halide, aryl anhydride, or aryl mixed anhydride, $A-C(O)-(CH_2)_n-Ar_2$. The reaction is carried out in a suitable solvent, such as tetrahydrofuran, N,N-dimethylaniline, or diethyl ether. The reaction is carried out in the presence of a base, such as N,N-dimethylaniline, sodium hydride, potassium t-butoxide, or lithium diisopropylamide. The reaction is generally carried out at temperatures of from -20°C to 50°C. Generally, the reactions require 1 to 24 hours. The product can be isolated and purified by techniques well known in the art, such as extraction, evaporation, trituration, chromatography, and recrystallization.

In Reaction Scheme J, optional step 3, an appropriate 5-oxo-3-aryl-3-acetic acid ester pyrrolidine of formula 36 is alkylated with an appropriate alkyl halide, $X-CH_2-(CH_2)_n-Ar_2$, to an N-arylalkyl-5-oxo-3-aryl-3-acetic acid ester pyrrolidine of formula 50. An appropriate alkyl halide, $X-CH_2-(CH_2)_n-Ar_2$, is one in which X is chloro, bromo, or iodo; n is as desired in the final product of formula (1), and Ar_2 is as desired in formula (1).

For example, an appropriate 5-oxo-3-aryl-3-acetic acid ester pyrrolidine of formula 36 is contacted with from 1.0 to 1.2 molar equivalents of an appropriate alkyl halide, $X-CH_2-(CH_2)_n-Ar_2$. The reaction is carried out in a suitable solvent, such as tetrahydrofuran, dimethyl sulfoxide, acetonitrile, or dimethylformamide. The reaction is carried out in the presence of a base, such as sodium hydride, sodium hexamethyldisilazide, potassium t-butoxide. The reaction is generally carried out at temperatures of from 0°C to 50°C. Generally, the reactions require 1 to 72 hours. The product can be isolated and purified by techniques well known in the art, such as extraction, evaporation, trituration, chromatography, and recrystallization.

In Reaction Scheme J, step 4, an appropriate N-arylalkyl-5-oxo-3-aryl-3-acetic acid ester pyrrolidine of formula 50 is hydrolyzed to give an N-arylalkyl-5-oxo-3-aryl-3-acetic acid pyrrolidine of formula 51.

For example, an appropriate N-arylalkyl-5-oxo-3-aryl-3-acetic acid ester pyrrolidine of formula 50 is contacted with a suitable hydrolyzing agent, such as sodium hydroxide, potassium hydroxide, or lithium hydroxide. The reaction is carried out in a suitable solvent such as water, tetrahydrofuran/water mixtures, methanol, methanol/water mixtures, or ethanol/water mixtures. The

reaction is generally carried out at temperatures of from 0°C to the refluxing temperature of the solvent.

Generally, the reactions require 1 to 72 hours. The
5 product can be isolated and purified by techniques well known in the art, such as extraction, evaporation, trituration, chromatography, and recrystallization.

In Reaction Scheme J, step 5, an appropriate N-
10 arylalkyl-5-oxo-3-aryl-3-acetic acid pyrrolidine of formula 51 is reduced to give a 5-oxo-3-aryl-3-(2-hydroxyethyl) pyrrolidine of formula 16.

For example, an appropriate 5-oxo-3-aryl-3-acetic acid
15 pyrrolidine of formula 51 is contacted with a suitable borane reagent, such as borane dimethyl sulfide complex. The reaction is carried out in a suitable solvent, such as tetrahydrofuran. The reaction is generally carried out at a temperature of from 0°C to the refluxing temperature of
20 the solvent. When complete, the reaction is quenched by the careful addition of a suitable aqueous acid solution, such as 1 M hydrochloric acid solution. The product can be isolated and purified by techniques well known in the art, such as extraction, evaporation, trituration,
25 chromatography, and recrystallization.

Alternately, an appropriate 5-oxo-3-aryl-3-acetic acid pyrrolidine of formula 51 can be reduced by formation of a mixed anhydride intermediate and contacting the mixed
30 anhydride intermediate with a suitable mild reducing agent, such as sodium borohydride to give 5-oxo-3-aryl-3-(2-hydroxyethyl) pyrrolidine of formula 16.

For example, an appropriate 5-oxo-3-aryl-3-acetic acid
35 pyrrolidine of formula 51 is contacted with 1.2 to 1.7 equivalents of a suitable base, such as N-methylmorpholine, in a suitable solvent, such as tetrahydrofuran or diethyl ether. The reaction mixture is cooled to a temperature of

between -50°C and 0°C with -25°C to -20°C being preferred, before the addition of 1.2 to 1.7 equivalents of isobutyl chloroformate. The reaction is allowed to stir for 30
5 minutes to 3 hours to allow for the formation of the mixed anhydride. After the formation of the mixed anhydride is complete, sodium borohydride is added. The product can be isolated and purified by techniques well known in the art, such as extraction, evaporation, chromatography, and
10 recrystallization.

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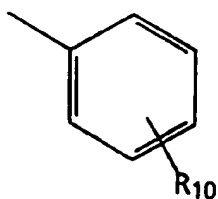
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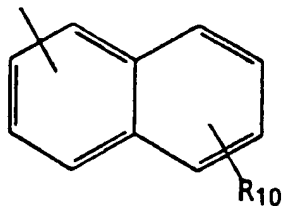
Reaction Scheme K

5 Reaction Scheme K is a general route for preparing some piperidine compounds of formula 18 which give rise to compounds of formula (1) in which Y_1 is $-C(O)NHR_5$, $-C(O)NR_6R_7$, or $-C(O)NR_8R_9$ and Y_2 is a radical chosen from the group

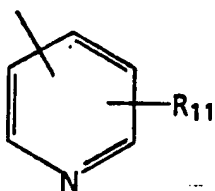
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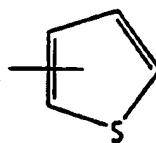
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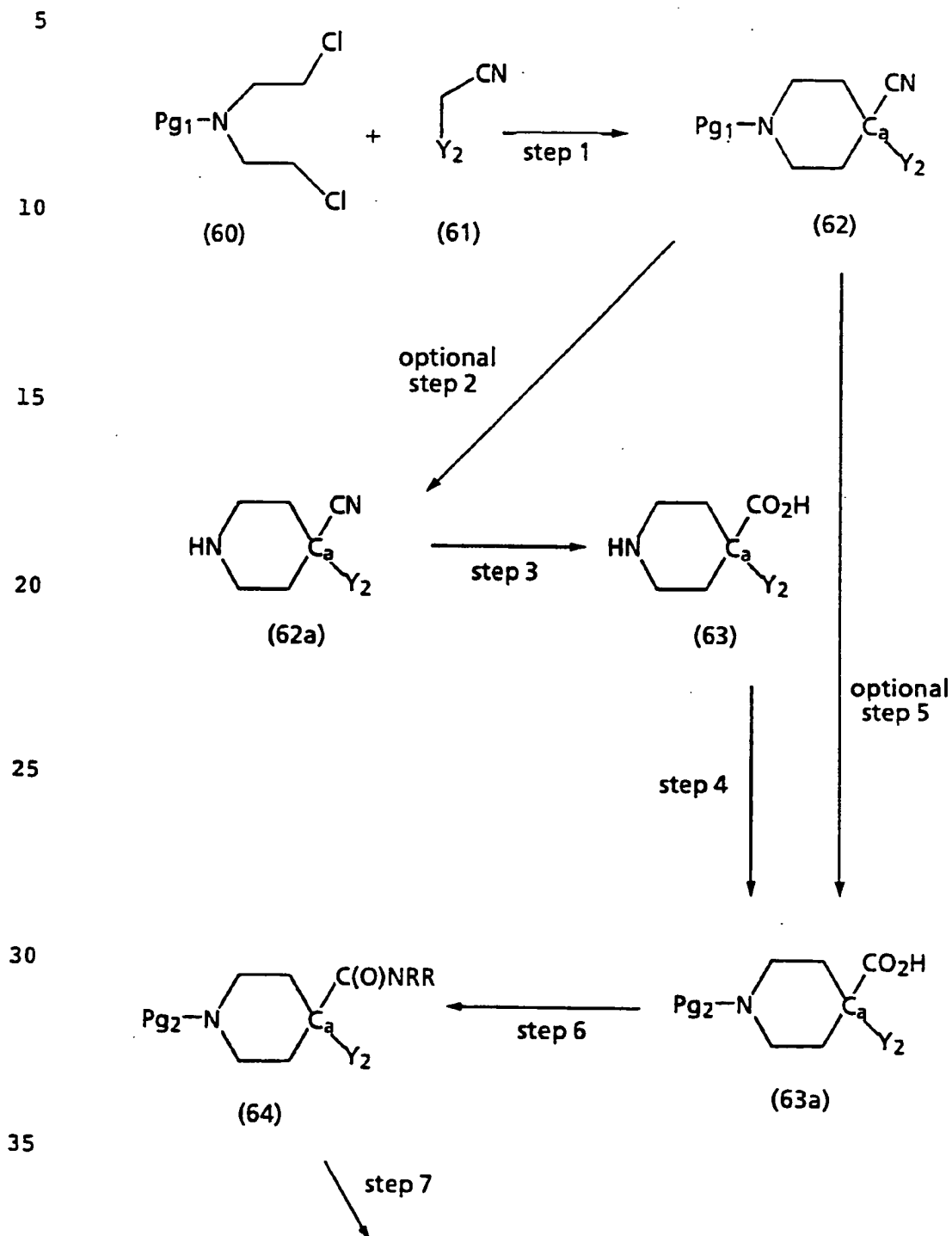
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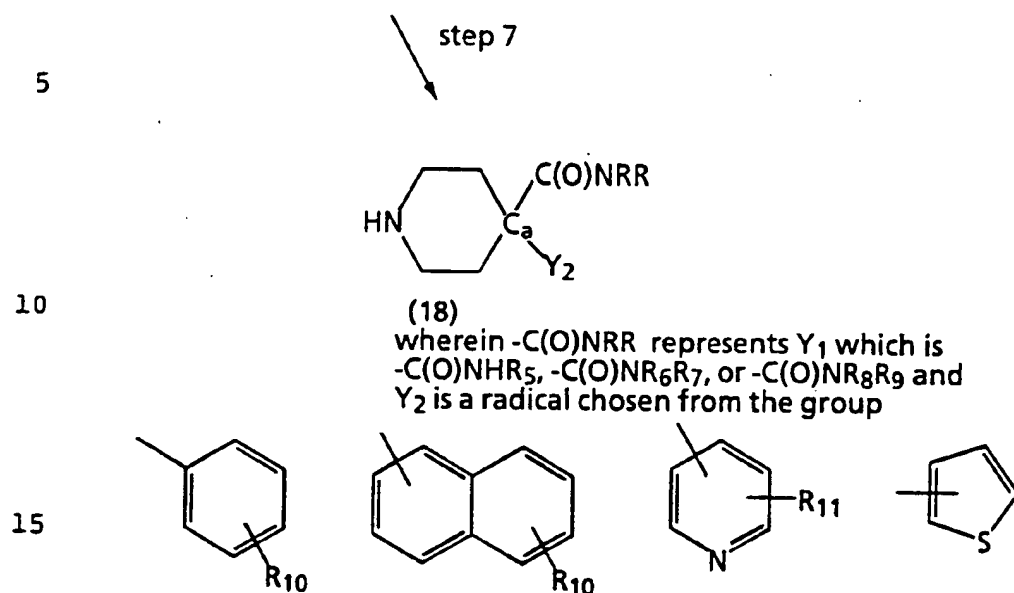
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Reaction Scheme K



Reaction Scheme K (Cont.)



20 In Reaction Scheme K, step 1, an appropriate protected bis-(2-chloroethyl)-amine of formula 60 is alkylated with an appropriate aryl acetonitrile of formula 61 to give an protected 4-aryl-4-cyano-piperidine of formula 62. An appropriate protected bis-(2-chloroethyl)-amine of formula

25 60 is one in which the protecting group, Pg₁, may be C₁-C₄ alkyl, benzyl, substituted benzyl, tosyl, benzenesulfonyl, or a carbamate, such as t-butoxycarbonyl or ethoxycarbonyl. An appropriate aryl acetonitrile of formula 61 is one in which Y₂ is as desired in the final product of formula (1).

30 Alkylations of this type are well known and appreciated in the art, T. Cammack and P. C. Reeves, J. Heterocyclic Chem. **23**, 73-75 (1986) and C. V. Bercz and R. D. Ice, J. Pharmaceutical Sci., **61**, 1316-1317 (1972).

35 For example, an appropriate protected bis-(2-chloroethyl)-amine of formula 60 is contacted with an appropriate aryl acetonitrile of formula 61. The reaction is carried out in the presence of a base, such as sodium

amide, sodium hydride, sodium hexamethyldisilazide, potassium t-butoxide, and lithium diisopropylamide. The reaction is carried out in a solvent, such as dimethyl sulfoxide and tetrahydrofuran. The reaction is generally carried out at temperatures of from 0°C to 80°C. Generally, the reactions require 1 to 72 hours. The product can be isolated and purified by techniques well known in the art, such as extraction, evaporation, trituration, chromatography, and recrystallization.

Alternately, for example, an appropriate protected bis-(2-chloroethyl)-amine of formula 60 is contacted with an appropriate aryl acetonitrile of formula 61 under phase transfer conditions. The reaction is carried out in a solvent system consisting of an organic phase and an aqueous phase. The reaction is carried out in the presence of a hydroxide base, such as sodium hydroxide or potassium hydroxide. The reaction is carried out in the presence of a suitable catalyst including quaternary ammonium and phosphonium salts, such as tetrabutylammonium bromide, tetrabutylammonium hydrogen sulfate, benzyltrimethylammonium chloride, hexadecyltributylphosphonium bromide, and the like. The reaction is vigorously stirred and is generally carried out at temperatures of between 0°C and 50°C. Generally, the reactions require 1 to 24 hours. The product can be isolated and purified by techniques well known in the art, such as extraction, evaporation, trituration, chromatography, and recrystallization.

In Reaction Scheme K, optional step 2, a protected 4-aryl-4-cyano-piperidine of formula 62 is deprotected to give a 4-aryl-4-cyano-piperidine of formula 62a. The removal of amine protecting groups is well known and appreciated in the art and is described in Protecting Groups in Organic Synthesis by T. Greene, Wiley-Interscience (1981). The removal of the amine protecting

group Pg₁, in this step may be required when Pg₁ is benzyl to allow the hydrolysis of the nitrile to the acid in step 3.

5

In Reaction Scheme K, step 3, a 4-aryl-4-cyano-piperidine of formula 62a is hydrolyzed to a 4-aryl-4-carboxylic acid-piperidine of formula 63. The hydrolysis of nitriles to acids may be carried out under acidic or
10 basic conditions as is well known and appreciated in the art.

In Reaction Scheme K, step 4, a 4-aryl-4-carboxylic acid-piperidine of formula 63 is protected to give a
15 protected 4-aryl-4-carboxylic acid-piperidine of formula 63a. The selection and use of amine protecting groups, Pg₂, is well known and appreciated in the art and is described in Protecting Groups in Organic Synthesis by T. Greene, Wiley-Interscience (1981).

20

In Reaction Scheme K, optional step 5, a protected 4-aryl-4-cyano-piperidine of formula 62 is hydrolyzed to a protected 4-aryl-4-carboxylic acid-piperidine of formula 63a. The hydrolysis of nitriles to acids may be
25 carried out under acidic or basic conditions as is well known and appreciated in the art. The selection and use of hydrolysis conditions which are compatible with the protecting groups, Pg₁, is well known and appreciated in the art. For protected 4-aryl-4-carboxylic acid-piperidine of
30 formula 63a prepared by Scheme K, optional step 5, the protecting groups Pg₁ and Pg₂ are necessarily the same protecting group.

In Reaction Scheme K, step 6, a protected 4-aryl-4-carboxylic acid-piperidine of formula 63a undergoes an
35 amidation reaction with an appropriate amine, NHRR, to give a protected 4-aryl-4-carboxylic acid amide-piperidine of formula 64. An appropriate amine, NHRR, includes amines of

the formulas NH_2R_5 , NHR_6R_7 , or NHR_8R_9 , in which R_5 , R_6 and R_7 , and R_8 and R_9 are as desired in the final compound of formula (1).

5

An amidation reaction may proceed through the acid of formula 63a or the acid function of a compound of formula 63a may be first converted to an activated intermediate; such as an anhydride; a mixed anhydride of substituted
10 phosphoric acid, such as dialkylphosphoric acid, diphenylphosphoric acid, halophosphoric acid; of aliphatic carboxylic acid, such as formic acid, acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, 2-ethylbutyric acid, trichloroacetic acid,
15 trifluoroacetic acid, and the like; of aromatic carboxylic acids, such as benzoic acid and the like; an activated ester, such as phenol ester, p-nitrophenol ester, 2,4-dinitrophenol ester, pentafluorophenol ester, pentachlorophenol ester, N-hydroxysuccinimide ester, N-
20 hydroxyphthalimide ester, 1-hydroxy-1H-benzotriazole ester, and the like; activated amide, such as imidazole, dimethylpyrazole, triazole, or tetrazole; or the intermediate formed in the presence of coupling agents, such as dicyclohexylcarbodiimide or 1-(3-
25 dimethylaminopropyl)-3-ethylcarbodiimide. Activated intermediates may be prepared and used directly, or are prepared and isolated before the addition of an appropriate amine, NHR of the formulas NH_2R_5 , NHR_6R_7 , or NHR_8R_9 . Alternately, activated intermediates may be prepared
30 isolated and purified before the addition of an appropriate amine, NHR of the formulas NH_2R_5 , NHR_6R_7 , or NHR_8R_9 . The use and formation of activated intermediates is well known and appreciated in the art.

35

For example, an acid compound of formula 63a is contacted with a slight molar excess of an appropriate amine, NHR of the formulas NH_2R_5 , NHR_6R_7 , or NHR_8R_9 , or a salt of an appropriate amine and 1-hydroxybenzotriazole

hydrate in the presence of a slight molar excess of a coupling agent, such as dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide. The reaction is
5 carried out in the presence of a suitable base, such as diisopropylethyl amine, if the salt of an amine is used an additional equimolar molar amount of a suitable base is added. The reaction is carried out in a suitable solvent, such as dichloromethane or chloroform. The product can be
10 isolated and purified by techniques well known in the art, such as extraction, evaporation, chromatography, and recrystallization.

Alternatively, for example, an acid of formula 63a is
15 contacted with 1.2 to 1.7 equivalents of a suitable base, such as N-methylmorpholine, in a suitable solvent, such as tetrahydrofuran. The reaction mixture is cooled to a temperature of between -50°C and 0°C with -25°C to -20°C being preferred, before the addition of 1.2 to 1.7
20 equivalents of isobutyl chloroformate. The reaction is allowed to stir for 30 minutes to 3 hours to allow for the formation of the mixed anhydride, an activated intermediate. While maintaining the temperature at between -50°C and 0°C an appropriate amine, NHRR of the formulas NH_2R_5 , NHR_6R_7 , or
25 NHR_8R_9 , is added, if the salt of an appropriate amine is used an additional equimolar molar amount of a suitable base is added. The reaction may, after the addition of amine is complete, be warmed to room temperature. Generally, the reaction requires from 2 to 48 hours. The product can be
30 isolated and purified by techniques well known in the art, such as extraction, evaporation, chromatography, and recrystallization.

In Reaction Scheme K, step 7 a protected 4-aryl-4-
35 carboxylic acid amide-piperidine of formula 64 is deprotected to give a piperidine of formula 18. The removal of amine protecting groups is well known and appreciated in the art and is described in Protecting

Groups in Organic Synthesis by T. Greene, Wiley-
Interscience (1981).

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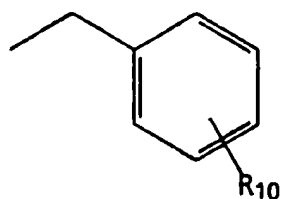
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Reaction Scheme L

5 Reaction Scheme L is a general route for preparing some
piperidine compounds of formula 18 which give rise to
compounds of formula (1) in which Y_1 is $-C(O)NHR_5$,
10 $-C(O)NR_6R_7$, or $-C(O)NR_8R_9$ and Y_2 is a radical chosen from
the group

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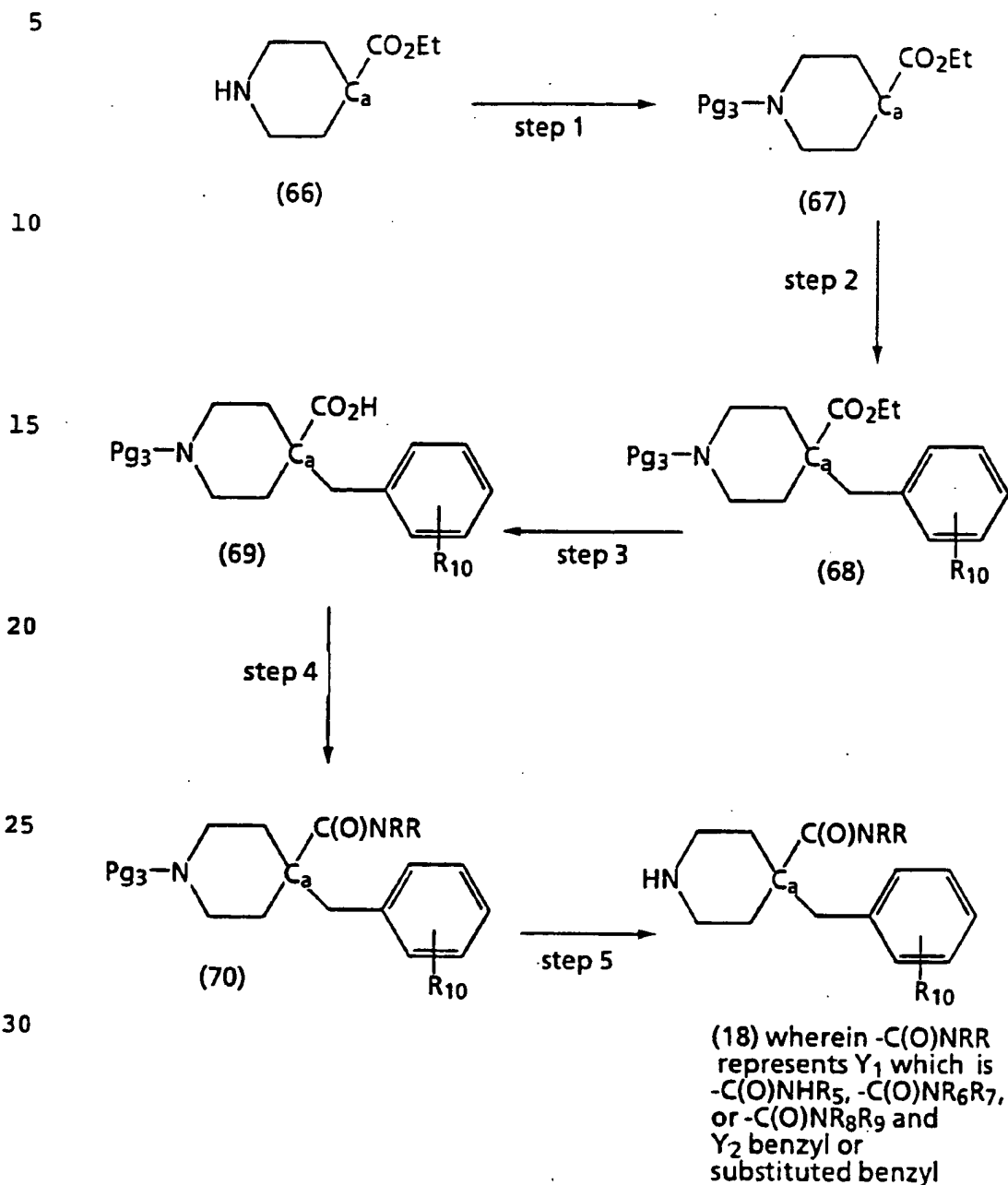
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Reaction Scheme L



In Reaction Scheme L, step 1, piperidine-4-carboxylic acid ethyl ester, compound 66 is protected to give a protected piperidine-4-carboxylic acid ethyl ester of

formula 67. The selection and use of amine protecting groups, Pg₃, is well known and appreciated in the art and is described in Protecting Groups in Organic Synthesis by T.

- 5 Greene, Wiley-Interscience (1981). The use of carbamate protecting groups, such as benzyloxycarbonyl and t-butoxycarbonyl is preferred.

In Reaction Scheme L, step 2, a protected piperidine-4-
10 carboxylic acid ethyl ester of formula 67 is reacted with an appropriate benzylating agent to give a protected 4-benzylated-piperidine-4-carboxylic acid ethyl ester of formula 68. An appropriate benzylating agent is one which transfers an benzyl or substituted benzyl in which R₁₀ is as
15 desired in the final product of formula (1).

For example, a protected piperidine-4-carboxylic acid ethyl ester of formula 67 is contacted with from 1.0 to 3.0 molar equivalents of benzyl halide or a substituted benzyl
20 halide. The reaction is carried out in the presence of 1.0 to 1.5 molar equivalents of a suitable base, such as sodium hexamethyldisilazide, sodium hydride, potassium t-butoxide, or lithium diisopropylamide. The reaction is carried out in a suitable solvent, such as tetrahydrofuran,
25 dimethylformamide, or dimethyl sulfoxide. The reaction is generally carried out at temperatures of from -78°C to 0°C. Generally, the reactions require 1 to 24 hours. The product can be isolated and purified by techniques well known in the art, such as extraction, evaporation,
30 trituration, chromatography, and recrystallization.

In Reaction Scheme L, step 3, a protected 4-benzylated-piperidine-4-carboxylic acid ethyl ester of formula 68 is hydrolyzed to give a protected 4-benzylated-piperidine-4-
35 carboxylic acid of formula 69.

For example, a protected 4-benzylated-piperidine-4-carboxylic acid ethyl ester of formula 68 is contacted with

a suitable hydrolyzing agent, such as sodium hydroxide, potassium hydroxide, or lithium hydroxide. The reaction is carried out in a suitable solvent such as water, tetrahydrofuran/water mixtures, methanol, methanol/water mixtures, or ethanol/water mixtures. The reaction is generally carried out at temperatures of from 0°C to the refluxing temperature of the solvent. Generally, the reactions require 1 to 72 hours. The product can be isolated and purified by techniques well known in the art, such as extraction, evaporation, trituration, chromatography, and recrystallization.

In Reaction Scheme L, step 4, a protected 4-benzylated-piperidine-4-carboxylic acid of formula 69 undergoes an amidation reaction; as generally taught in Reaction Scheme K, step 6; with an appropriate amine, NHRR, to give a protected 4-benzylated-piperidine-4-carboxylic acid amide of formula 70. An appropriate amine, NHRR, includes amines of the formulas NH_2R_5 , NHR_6R_7 , or NHR_8R_9 , in which R_5 , R_6 and R_7 , and R_8 and R_9 are as desired in the final compound of formula (1).

In Reaction Scheme L, step 5, a protected 4-benzylated-piperidine-4-carboxylic acid amide of formula 70 is deprotected to give a 4-benzylated-piperidine-4-carboxylic acid amide of formula 18 in which Y_1 is $-\text{C}(\text{O})\text{NHR}_5$, $-\text{C}(\text{O})\text{NR}_6\text{R}_7$, or $-\text{C}(\text{O})\text{NR}_8\text{R}_9$ and Y_2 benzyl or substituted benzyl. The removal of amine protecting groups is well known and appreciated in the art and is described in Protecting Groups in Organic Synthesis by T. Greene, Wiley-Interscience (1981).

Reaction Scheme M

5 Reaction Scheme M is a general routes for preparing
piperidine compounds of formula 18 which give rise to
compounds of formula (1) in which Y₁ and Y₂ together with
their attached carbon form a spirocyclic ring chosen from
the group

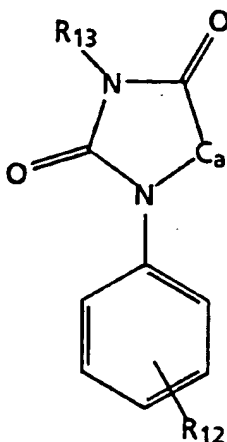
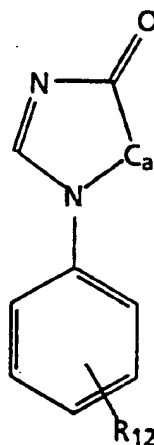
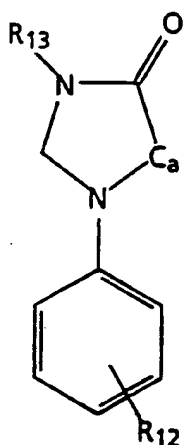
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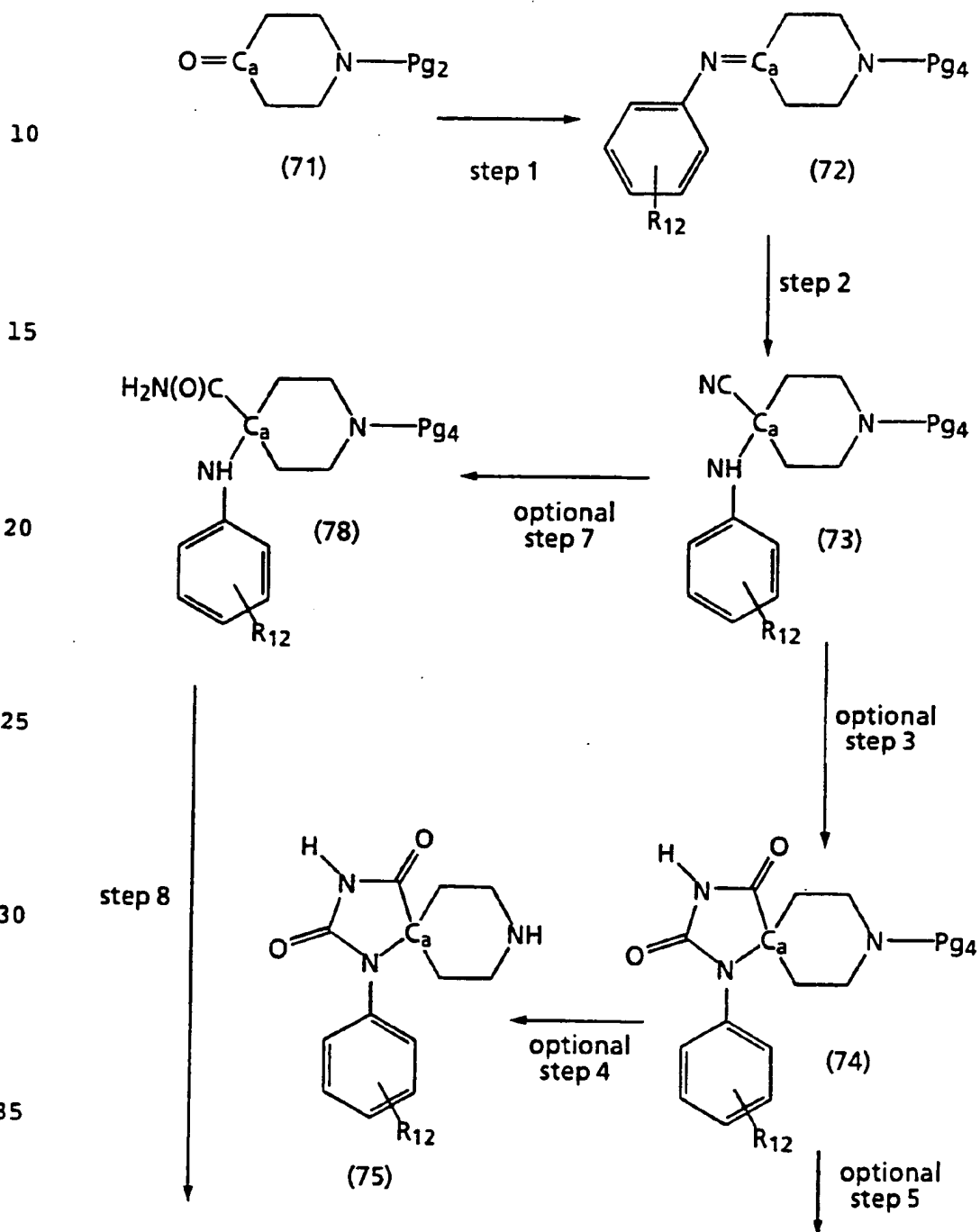
30



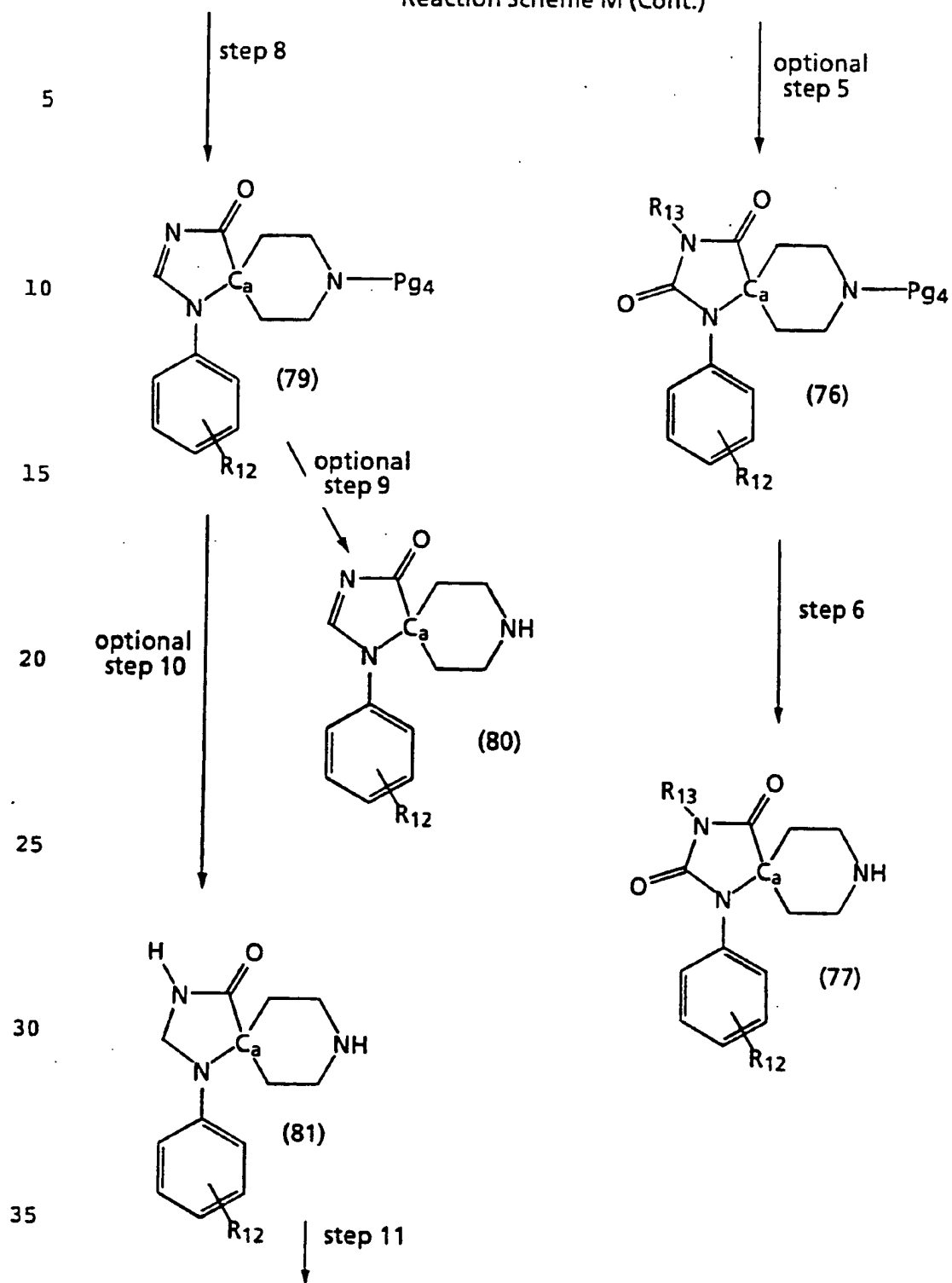
Some of the piperidine compounds of formula 18 in which Y₁
and Y₂ together with their attached carbon form a
spirocyclic ring are known in the art or can be prepared by
methods known analogously in the art. P. L. Feldman and M.
35 F. Bracken JOC 55, 4207-4209 (1990); L. D. Wise et al. J.
Med. Chem. 28, 1811-1817 (1985); and G. M. Carrera, Jr. and
D. S. Garvey, J. Heterocyclic Chem. 29, 847-850 (1992).

Reaction Scheme M

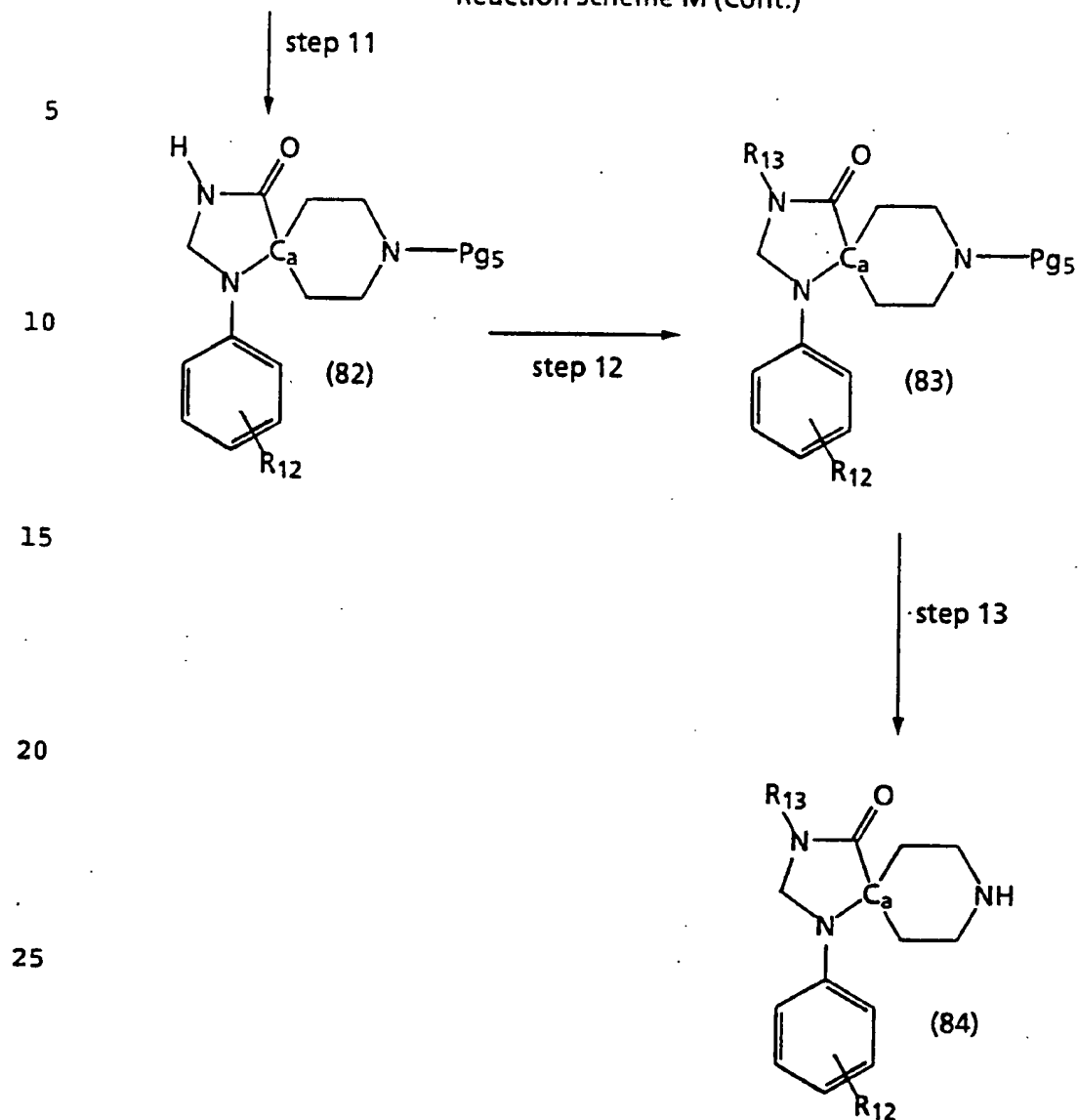
5



Reaction Scheme M (Cont.)



Reaction Scheme M (Cont.)



In Reaction Scheme M, step 1, a protected piperidin-4-one of formula 71 is condensed with the appropriate aniline to give a protected imine of formula 72. An appropriate aniline is one in which gives rise to an imine of formula 72 in which R₁₂ is as is desired in the final compound of formula (1). Generally, the protected imine of formula 72 is not isolated before it is converted to the protected 4-

cyano piperidine of formula 73. The formation of protected imines of formula 72 is well known and appreciated in the art.

5

In Reaction Scheme M, step 2, a protected imine of formula 72 is converted to a protected 4-cyano piperidine of formula 73. A protected imine of formula 72 is contacted with a reagent which causes it to undergo a
10 Strecker reaction, such as hydrogen cyanide, potassium cyanide, sodium cyanide, acetone cyanohydrin, or trimethylsilyl cyanide. The conditions used depend on the method chosen for carrying out the Strecker reaction. The
15 Strecker reaction and the choice of conditions for carrying out the Strecker reaction are well known and appreciated in the art.

In Reaction Scheme M, optional step 3, a protected 4-cyano piperidine of formula 73 is converted to a protected
20 1-phenyl-1,3,8-triazaspiro[4.5]decane-2,4-dione of formula 74.

For example, a protected 4-cyano piperidine of formula 73 is contacted with an equimolar amount of chlorosulfonyl
25 isocyanate to give an unpurified intermediate. The reaction is carried out in a suitable solvent, such as dichloromethane. Generally, the reaction is carried out at temperatures of from 0°C to 50°C. The reaction generally requires from 10 minutes to 3 hours. The unpurified
30 intermediate is recovered by evaporation *in vacuo*. The unpurified intermediate is contacted with a suitable aqueous acid, such as 1 M hydrochloric acid, and is heated to from 50°C to the refluxing temperature of the suitable aqueous acid. The reaction generally requires from 30
35 minutes to 4 hours. The product can be isolated and purified by techniques well known in the art, such as cooling, adjusting of pH, extraction, evaporation, chromatography, and recrystallization.

In Reaction Scheme M, optional step 4, a protected 1-phenyl-1,3,8-triazaspiro[4.5]decane-2,4-dione of formula 74 is deprotected to give a 1-phenyl-1,3,8-triazaspiro[4.5]decane-2,4-dione of formula 75. The removal of amine protecting groups is well known and appreciated in the art and is described in Protecting Groups in Organic Synthesis by T. Greene, Wiley-Interscience (1981); R. A Olofson, JOC 49, 2936-2938 (1991); and Y-K. Shue et al., JOC 56, 2936-2938 (1991).

In Reaction Scheme M, optional step 5, a protected 1-phenyl-1,3,8-triazaspiro[4.5]decane-2,4-dione of formula 74 is benzylated or alkylated with an appropriate benzylating or alkylating agent to give a protected 3-substituted-1-phenyl-1,3,8-triazaspiro[4.5]decane-2,4-dione of formula 76. An appropriate benzylating or alkylating agent is one which transfers a benzyl, substituted benzyl, or C₁-C₆ alkyl as is required in R₁₃ in the final product of formula (1).

For example, a protected 1-phenyl-1,3,8-triazaspiro[4.5]decane-2,4-dione of formula 74 is contacted with 1.0 to 3.0 molar equivalents of an appropriate benzylating or alkylating agent, such as benzyl halide, a substituted benzyl halide, or a C₁-C₆ alkyl halide. The reaction is carried out in the presence of 1.0 to 1.5 molar equivalents a suitable base, such as sodium hydroxide, potassium hydroxide, sodium hexamethyldisilazide, sodium hydride, potassium t-butoxide, or lithium diisopropylamide. The reaction is carried out in a suitable solvent, such as tetrahydrofuran, ethanol, dimethylformamide, or dimethyl sulfoxide. The reaction is generally carried out at temperatures of from 0°C to the refluxing temperature of the solvent. Generally, the reactions require 1 to 24 hours. The product can be isolated and purified by techniques well known in the art, such as extraction,

evaporation, trituration, chromatography, and recrystallization.

5 In Reaction Scheme M, step 6, a protected 3-substituted-1-phenyl-1,3,8-triazaspiro[4.5]decane-2,4-dione of formula 76 is deprotected to give a 3-substituted-1-phenyl-1,3,8-triazaspiro[4.5]decane-2,4-dione of formula 77. The removal of amine protecting groups is well known
10 and appreciated in the art and is described in Protecting Groups in Organic Synthesis by T. Greene, Wiley-Interscience (1981); R. A Olofson, JOC 49, 2936-2938 (1991); and Y-K. Shue et al., JOC 56, 2936-2938 (1991).

15 In Reaction Scheme M, optional step 7, a protected 4-cyano-piperidine of formula 73 is hydrolyzed to give a protected piperidine-4-carboxylic acid amide of formula 78. The hydrolysis of nitriles to carboxylic acid amides under acidic conditions is well known and appreciated in the art.

20 In Reaction Scheme M, step 8, a protected piperidine-4-carboxylic acid amide of formula 78 is converted to a protected 1-phenyl-1,3,8-triazaspiro[4.5]dec-2-en-4-one of formula 79.

25 For example, a protected piperidine-4-carboxylic acid amide of formula 78 is contacted with an excess of dimethoxy-N,N-dimethylmethanamine. The reaction is carried out in a suitable solvent, such as toluene. Generally, the
30 reaction is carried out at temperatures of from ambient temperature to the refluxing temperature of the solvent. The reactions generally require from 12 to 72 hours. The product can be isolated and purified by techniques well known in the art, such as extraction, evaporation,
35 trituration, chromatography, and recrystallization.

 In Reaction Scheme M, optional step 9, a protected 1-phenyl-1,3,8-triazaspiro[4.5]dec-2-en-4-one of formula 79

is deprotected to give a 1-phenyl-1,3,8-triazaspiro[4.5]dec-2-en-4-one of formula 80. The removal of amine protecting groups is well known and appreciated in the art and is described in Protecting Groups in Organic Synthesis by T. Greene, Wiley-Interscience (1981); R. A Olofson, JOC 49, 2936-2938 (1991); and Y-K. Shue et al., JOC 56, 2936-2938 (1991).

10 In Reaction Scheme M, optional step 10, a protected 1-phenyl-1,3,8-triazaspiro[4.5]dec-2-en-4-one of formula 79 is reduced to a 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one of formula 81 or a protected 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one of formula 82. A 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one of formula 81 is the product of Reaction Scheme M, optional step 10, when Pg₄ is a protecting group which is removed by hydrogenation, such as benzyl or substituted benzyl. A protected 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one of formula 82 is the product of Reaction Scheme M, optional step 10, when a hydrogenation stable protecting group, such as methyl is used. For protected 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one of formula 82 prepared by Scheme M, optional step 10, the protecting groups Pg₄ and Pg₅ are necessarily the same protecting group.

For example, a protected 1-phenyl-1,3,8-triazaspiro[4.5]dec-2-en-4-one of formula 79 is contacted with hydrogen in the presence of a suitable catalyst, such as 5% platinum-on-carbon, 10% platinum-on-carbon, 5% palladium-on-carbon, 10% palladium-on-carbon, Pearlman's catalyst, platinum oxide, and palladium oxide. The reaction is carried out in a suitable solvent, such as ethanol, methanol, ethyl acetate, and water. The reaction is generally carried out at temperatures of from ambient temperature to 50°C. The reaction is carried out at pressures of from 15 psi to 120 psi in an apparatus designed for carrying out reactions under pressure, such as

a Parr hydrogenation apparatus. The product can be isolated by carefully removing the catalyst by filtration and evaporation. The product can be purified by
5 extraction, evaporation, trituration, chromatography, and recrystallization.

In Reaction Scheme M, step 11, a 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one of formula 81 is protected to
10 give a protected a 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one of formula 82. The selection and use of suitable amine protecting groups is well known and appreciated in the art and is described in Protecting Groups in Organic Synthesis by T. Greene, Wiley-Interscience (1981).

15

In Reaction Scheme M, step 12, a protected 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one of formula 82 is is
benzylated or alkylated with an appropriate benzylating or alkylating agent to give a protected 3-substituted-1-
20 phenyl-1,3,8-triazaspiro[4.5]decan-4-one of formula 83. An appropriate benzylating or alkylating agent is one which transfers a benzyl, substituted benzyl, or C₁-C₆ alkyl as is required in R₁₃ in the final product of formula (1).

25 For example, a protected 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one of formula 82 is contacted with 1.0 to 3.0 molar equivalents of an appropriate benzylating or alkylating agent, such as benzyl halide, a substituted benzyl halide, or a C₁-C₆ alkyl halide. The reaction is
30 carried out in the presence of 1.0 to 1.5 molar equivalents a suitable base, such as sodium hexamethyldisilazide, sodium hydride, potassium t-butoxide, or lithium diisopropylamide. The reaction is carried out in a suitable solvent, such as tetrahydrofuran,
35 dimethylformamide, or dimethyl sulfoxide. The reaction is generally carried out at temperatures of from -10°C to the refluxing temperature of the solvent. Generally, the reactions require 1 to 72 hours. The product can be

isolated and purified by techniques well known in the art, such as extraction, evaporation, trituration, chromatography, and recrystallization.

5

In Reaction Scheme M, step 13, a protected 3-substituted-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one of formula 83 is deprotected to give a 3-substituted-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one of formula 84. The
10 removal of amine protecting groups is well known and appreciated in the art and is described in Protecting Groups in Organic Synthesis by T. Greene, Wiley-Interscience (1981).

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Example 1:

Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-benzoyl-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide

10

1.1 Synthesis of 3-cyano-3-(3,4-dichloro-phenyl)-pentanedioic diethyl ester (No.027F126)

3,4-Dichlorophenylacetonitrile (10 g, 53.75 mmol) was stirred mechanically in THF (50 mL) at -78°C and treated dropwise with sodium bis-(trimethylsilyl)amide (108 mL, 1 M; 2 eq.). The reaction slurry was allowed to warm to 20°C and stirred for 3 hours. The solution was cooled to -78°C and the slurry was treated with ethyl bromoacetate (12 mL, 107 mmol, 2 eq.). The slurry was again allowed to warm to 20°C and stirred 18 hours. The slurry was dissolved in ethyl ether and washed with water and brine. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (400 g) with 20% ethyl acetate to give 15.85 g (82%) of the title compound.

1.1.2 Synthesis of 3-cyano-3-(3,4-dichloro-phenyl)-pentanedioic acid diethyl ester

30

3,4-Dichlorophenylacetonitrile (30.0 g, 0.161 mol) and THF (100 mL) were combined and cooled in a dry-ice/acetone bath. Sodium bis-(trimethylsilyl)amide (324 mL, 1.0 M in THF, 0.324 mol, 2 eq.) was added dropwise. After the addition was complete, the mixture was allowed to warm to ambient temperature. After 4 h, the mixture was cooled in a dry-ice/acetone bath. Ethyl bromoacetate (36 mL, 0.325 mol) was added dropwise. After the addition was complete,

the mixture was allowed to warm to ambient temperature.

The reaction mixture was partitioned between diethyl ether and water. The organic layer was extracted with H₂O (3 X 150 mL), 1N HCl (2 X 100 mL), 5% NaHCO₃ (2 X 100 mL), and brine (1 X 150 mL). The organic layer was dried over MgSO₄, filtered, and concentrated *in vacuo* to obtain a residue. The residue was recrystallized from diethyl ether to give the title compound:

10 R_f=0.28 (silica gel, 20% ethyl acetate in hexane), mp=68-69°C.

Analysis: calculated for C₁₆H₁₇Cl₂NO₄ C 53.65; H 4.78; N 3.91; Found C 53.69; H 4.79; N 3.93.

15

1.2 Synthesis of [3-(3,4-dichloro-phenyl)-5-oxo-pyrrolidin-3-yl]-acetic acid ethyl ester
(No.027F128)

20 3-Cyano-3-(3,4-dichloro-phenyl)-pentanedioic acid diethyl ester (10 g; 27.94 mmol) was dissolved in methanol (100 mL) and cobalt(II)chloride hexahydrate (13.2 g, 55.48 mmol) was added. The solution was then cautiously treated with one gram portions of sodium borohydride (11 g, 290
25 mmol) over 45 minutes at 20-30°C. The solution was allowed to stir an additional 1.5 hours and the solution was concentrated *in vacuo*. The residue was partitioned between dichloromethane and 1 N HCl the organic phase was and washed with 1N HCl (700 mL). The organic phase was dried
30 over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (600 g) with a gradient of 3% to 6% methanol in dichloromethane to give 7.514 g (85%) of the title compound.

35

1.2.2 Synthesis of [3-(3,4-dichloro-phenyl)-5-oxo-pyrrolidin-3-yl]-acetic acid ethyl ester

- 5 3-Cyano-3-(3,4-dichloro-phenyl)-pentanedioic acid diethyl ester (32 g, 89.4 mmol) and ethanol (150 mL) were combined. The mixture was added to Raney nickel (100 g) in a Parr bottle and NH_4OH (40 mL) was added. The reaction was hydrogenated in a Parr shaker at 50 psi for 24 h. The
10 slurry was filtered through a celite pad and the solids were rinsed with ethanol. The filtrate was concentrated *in vacuo* to obtain a residue. The residue was chromatographed on silica gel (400 g) eluting with 6% methanol in dichloromethane to give the title compound:
15 $R_f=0.34$ (silica gel, 6% methanol in dichloromethane), mp=87-90°C.
Analysis: calculated for $\text{C}_{14}\text{H}_{15}\text{Cl}_2\text{NO}_3$ C 53.18; H 4.78; N 4.43; Found C 53.34; H 4.71; N 4.51.

20 1.3 Synthesis of [3-(3,4-dichloro-phenyl)-3-(2-hydroxy-ethyl)-pyrrolidine (No.027F129)

- Lithium aluminum hydride (4.0 g, 105 mmol) was stirred in THF (20 mL) and [3-(3,4-dichloro-phenyl)-5-oxo-
25 pyrrolidiny-3-yl]-acetic acid ethyl ester (7.51 g, 23.79 mmol) was added dropwise in THF (50 mL). The slurry was heated to reflux and allowed to stir for 21 hours. The slurry was cooled in an ice bath and sequentially treated dropwise with water (4 mL), 15% NaOH (4 mL), and water (12
30 mL). The slurry was allowed to stir for 3 hours at 20°C. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 6.37 g of the title compound.

1.3.2 Synthesis of 2-[3-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethanol

5 A solution of LiAlH_4 (450 mL, 1M in THF, 450 mmol) was cooled in a ice/acetone bath (-10°C). A solution of H_2SO_4 (99.999%) (12 mL, 225.3 mmol) in THF (35 mL) was added dropwise. (Use caution when adding the H_2SO_4 to the THF and also when adding the $\text{H}_2\text{SO}_4/\text{THF}$ solution to the LiAlH_4 .)

10 After the addition was complete, the slurry was stirred for 1 h in an ice bath. The slurry was allowed to warm to ambient temperature and stir for 2 h. A solution of [3-(3,4-dichloro-phenyl)-5-oxo-pyrrolidin-3-yl]-acetic acid ethyl ester (23.2 g, 73.4 mmol) in THF (70 mL) was added

15 dropwise. The slurry was heated to $45-50^\circ\text{C}$ for 36 h. The slurry was cooled in an ice bath and a solution of $\text{THF}:\text{H}_2\text{O}$ (1:1, 70 mL) was added dropwise. The slurry was filtered and the solids were rinsed with THF and dichloromethane. The salts were stirred with $\text{THF}:\text{H}_2\text{O}:15\% \text{ NaOH}$ (1 L :70 mL :20

20 mL) for 2 h. The slurry was filtered and the combined filtrates were concentrated *in vacuo* to obtain a residue. The residue was dissolved in dichloromethane and the solution was dried over MgSO_4 , filtered, and concentrated *in vacuo* to obtain a residue. The residue was recrystallized

25 from diethyl ether to give the title compound:
 $R_f=0.27$ (silica gel, 9:1:0.2;
dichloromethane:methanol:ammonium hydroxide), $\text{mp}=91-94^\circ\text{C}$.
Analysis: calculated for $\text{C}_{12}\text{H}_{15}\text{Cl}_2\text{NO}$ C 55.40; H 5.81; N 5.38; Found C 55.64; H 5.88; N 5.20.

30

1.4 Synthesis of [3-(3,4-dichloro-phenyl)-1-(benzoyl)-3-(2-hydroxy-ethyl)-pyrrolidine (No.027F114)

3-(3,4-Dichloro-phenyl)-3-(2-hydroxy-ethyl)-pyrrolidine

35 (6.37 g, 24.5 mmol) was dissolved in dichloromethane (100 mL) at -78°C and treated with 4-methylmorpholine (5.5 mL, 50 mmol, 2.0 eq.) and benzoyl chloride (3.0 mL, 25.8 mmol, 1.05 eq.). The solution was allowed to warm to 0°C and stir

for 2 hours. The reaction mixture was washed with 1N HCl and 5% NaHCO₃, and the organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (300 g) with a gradient from ethyl acetate to 10% methanol in dichloromethane to give 6.32 g (71%) of the title compound.

1.5 Synthesis of 2-[1-benzoyl-3-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate (No.027F42)

3-(3,4-Dichloro-phenyl)-1-(benzoyl)-3-(2-hydroxy-ethyl)-pyrrolidine (220 mg, 0.6 mmol) was dissolved in dichloromethane (4 mL) and N,N-diisopropylethylamine (0.13 mL, 0.75 mmol, 1.24 eq.) and methanesulfonyl chloride (0.055 mL, 0.71 mmol, 1.18 eq.) were added at 0°C. The solution was allowed to stir at 0°C for 3 hours. The solution was diluted with dichloromethane and washed with 1 N HCl, 5% sodium bicarbonate and water. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (30 g), with a gradient of 50% ethyl acetate in hexane to 75% ethyl acetate in hexane to give 191 mg (72%) of the title compound.

1.6 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide (No.027F42)

2-[1-Benzoyl-3-(3,4-dichloro-phenyl)-pyrrolidin-3-yl] ethyl methanesulfonate (191 mg, 0.43 mmol) was treated with the 4-phenyl-piperidine-4-carboxylic acid amide hydrochloride (144 mg, 0.599 mmol) and NaHCO₃ (90 mg, 1.07 mmol, 2.5 eq.) in THF/H₂O (5 mL/1 mL) at reflux for 21 hours. The solution was concentrated *in vacuo* and the aqueous phase was extracted with dichloromethane. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was chromatographed

on silica gel (30 g) with 6% methanol in dichloromethane to give 146 mg (44%).

- 5 Exact mass (Cl): calculated for $C_{31}H_{33}Cl_2N_3O_2(M^+)$: 549.1950.
Found 549.1920.

Example 2

- 10 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(2,4-
dimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-
piperidine-4-carboxylic acid amide

- 2.1 Synthesis of [3-(3,4-dichloro-phenyl)-1-(2,4-
15 dimethoxy-benzoyl)-3-(2-hydroxy-ethyl)-pyrrolidine
 (No.027F108)

3-(3,4-Dichloro-phenyl)-3-(2-hydroxy-ethyl)-pyrrolidine
(288 mg, 1.1 mmol) was dissolved in dichloromethane (3 mL)
20 at -78°C and treated with 4-methylmorpholine (0.25 mL, 2.27
mmol, 2.eq.) and 2,4-dimethoxy-benzoyl chloride (220 mg,
1.1 mmol, 1 eq.) dissolved in 3 mL of dichloromethane. The
solution was allowed to warm to 0°C and stirred for 1 hour.
The solution was washed with 1N HCl, and 5% sodium
25 bicarbonate. The organic phase was dried over magnesium
sulfate, filtered, and concentrated *in vacuo*. The residue
was chromatographed on silica gel (30 g) with a gradient of
50% ethyl acetate in hexane to 6% methanol in
dichloromethane to give 324 mg (69%) of the title compound.

30

- 2.2 Synthesis of 2-[1-(2,4-dimethoxy-benzoyl)-3-(3,4-
dichloro-phenyl)-pyrrolidin-3-yl]-ethyl-
methanesulfonate (No.027F117)

- 35 3-(3,4-Dichloro-phenyl)-1-(2,4-dimethoxy-benzoyl)-3-(2-
hydroxy-ethyl)-pyrrolidine (320 mg, 0.75 mmol) was
dissolved in dichloromethane (5 mL) and N,N-
diisopropylethylamine (0.35 mL, 2.0 mmol, 2.7 eq.) and

methanesulfonyl chloride (0.080 mL, 1.0 mmol, 1.4 eq.) were added dropwise at 0°C and allowed to stir for 3 hours. The solution was diluted with dichloromethane and washed with 1 N HCl and 5% sodium bicarbonate. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (30 g) with 6% methanol in dichloromethane to give 343 mg (91%) of the title compound.

2.3 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(2,4-dimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide
(No.027F117).

2-[1-(2,4-Dimethoxy-benzoyl)-3-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate (343 mg, 0.68 mmol) was dissolved in THF (8 mL) and the 4-phenyl-piperidine-4-carboxylic acid amide hydrochloride (170 mg, 0.71 mmol, 1.04 eq.), potassium carbonate (200 mg, 1.45 mmol, 2.1 eq.), and water (2 mL) were added and the solution was heated at reflux for 16 hours. The solution was concentrated *in vacuo* and the aqueous phase was extracted with dichloromethane, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (40 g) with a gradient of ethyl acetate to 6% methanol in dichloromethane to give 151 mg (36%) of the title compound.

Analysis: calculated for $C_{33}H_{37}Cl_2N_3O_4 \cdot 0.6 H_2O$ C 63.86; H 6.20; N 6.76. Found C 63.61; H 6.13; N 6.67.

Example 3

5 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-
 trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-
 piperidine-4-carboxylic acid amide

10 3.1 Synthesis of [3-(3,4-dichloro-phenyl)-1-(3,4,5-
 trimethoxy-benzoyl)-3-(2-hydroxy-ethyl)-pyrrolidine
 (No.027F109)

 3-(3,4-Dichloro-phenyl)-3-(2-hydroxy-ethyl)-pyrrolidine
 (288 mg, 1.1 mmol) was dissolved in dichloromethane at
 -78°C and treated with 4-methylmorpholine (0.25 mL, 2.27
15 mmol, 2 eq.) and 3,4,5-trimethoxy-benzoyl chloride (250 mg,
 1.1 mmol, 1 eq) in dichloromethane (3 mL). The solution
 was allowed to warm to 0°C and stir for 1 hour. The
 solution was washed with 1N HCl and 5% sodium bicarbonate
 and the organic phase was dried over magnesium sulfate,
20 filtered, and concentrated *in vacuo*. The residue was
 chromatographed on silica gel (30 g) with a gradient of 50%
 ethyl acetate in hexane to 6% methanol in dichloromethane
 to give 353 mg (71%) of the title compound.

25 3.1.1 Synthesis of 2-[3-(3,4-dichloro-phenyl-3-yl)-1-
 (3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethanol

 2-[3-(3,4-Dichloro-phenyl)-pyrrolidin-3-yl]-ethanol
 (5.885 g, 22.64 mmol) and dichloromethane (135 mL) were
30 combined. 4-Methylmorpholine (5.0 mL , 45.48 mmol, 2 eq.)
 was added. The mixture was cooled in a dry-ice/acetone
 bath and a solution of 3,4,5-trimethoxy-benzoyl chloride
 (5.22 g, 22.63 mmol) in dichloromethane (100 mL) was added
 dropwise. After the addition was complete, the dry-
35 ice/acetone bath was changed to an ice bath and the mixture
 was stirred for 1 h. The solution was extracted with 1N
 HCl (50 mL), 5% NaHCO₃ (50 mL), and H₂O (50 mL) . The
 organic phase was dried over MgSO₄, filtered, and

concentrated *in vacuo* to obtain a residue. The residue was purified by chromatography on silica gel (400 g) eluting with ethyl acetate and then 6% methanol in dichloromethane to give the title compound:
R_f=0.38 (silica gel, 6% methanol in dichloromethane).

3.2 Synthesis of 2-[3,4-(dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl] ethyl methanesulfonate (No.027F116)

3-(3,4-Dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-3-(2-hydroxy-ethyl)-pyrrolidine (350 mg, 0.77 mmol), was dissolved in dichloromethane (5 mL) and N,N-diisopropylethylamine (0.35 mL, 2.0 mmol, 2.6 eq.) and methanesulfonyl chloride (0.080 mL, 1.03 mmol, 1.34 eq.) were added dropwise at 0°C. The solution was allowed to stir for 1 hour at 0°C. The solution was diluted with dichloromethane and washed with 1 N HCl and 5% sodium bicarbonate. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (30 g) with a gradient of ethyl acetate to 6% methanol in dichloromethane to give 376 mg (92%) of the title compound.

3.2.1 Synthesis of 2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate

2-[3-(3,4-Dichloro-phenyl-3-yl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethanol (3.5 g, 7.87 mmol) and dichloromethane (100 mL) were combined. N,N-diisopropylethylamine (3.0 mL, 17.22 mmol, 2.2 eq.) was added and the mixture was cooled in an ice bath. Methanesulfonyl chloride (0.82 mL, 10.59 mmol, 1.35 eq.) was added dropwise. After the addition, the mixture was stirred 1.5 h. Methanesulfonyl chloride (0.05 mL, 0.65

mmol, 0.08 eq.) was added dropwise. After the addition, the mixture was stirred 0.5 h. The solution was extracted with 1N HCl (2 X 100 mL) and 5% NaHCO₃ (100 mL). The organic phase was dried over MgSO₄, filtered, and concentrated *in vacuo* to obtain a residue. The residue was dried under high vacuum at ambient temperature for 18 h to give the title compound:

R_f=0.27 (silica gel, ethyl acetate).

3.3 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide (No.027F116)

2-[3,4-(Dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate, (376 mg, 0.707 mmol) was dissolved in THF (8 mL) and 4-phenyl-piperidine-4-carboxylic acid amide hydrochloride (170 mg, 0.707 mmol, 1 eq.), potassium carbonate (200 mg, 1.45 mmol, 2 eq.), and water (2 mL), were added and the solution was heated at reflux for 16 h. The solution was concentrated *in vacuo* and the aqueous phase was extracted with dichloromethane. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (40 g) with a gradient of ethyl acetate to 6% methanol in dichloromethane to isolate the the title compound. The residue was dissolved in dichloromethane and added dropwise into a saturated ether/HCl solution. The slurry was concentrated *in vacuo* and the residue was dried under high vacuum at 50°C to give the hydrochloride salt of the title compound 321 mg (71%).

Analysis: calculated for C₃₄H₃₉Cl₂N₃O₅ · HCl · 0.5 H₂O: C 62.93; H 6.21; N 6.48. Found C 62.86; H 6.19; N 6.30.

3.3.1 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl-3-yl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide

5

2-[3-(3,4-Dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate (7.87 mmol) and THF/H₂O (3/1, 80 mL) were combined. 4-Phenyl-piperidine-4-carboxylic acid amide hydrochloride (2.8 g, 11.64 mmol, 1.5 eq.) and potassium carbonate (3.3 g, 23.88 mmol, 3 eq.) were added. The mixture was heated to reflux for 72 h. The mixture was concentrated *in vacuo*. The aqueous residue was extracted with dichloromethane. The organic phase was extracted with H₂O (50 mL). The organic phase was dried over MgSO₄, filtered, and concentrated *in vacuo* to obtain a residue. The residue was purified by chromatography on silica gel (350 g) eluting sequentially with ethyl acetate, 6% methanol in dichloromethane, and then 10% methanol in dichloromethane to give the title compound:

15
20

R_f=0.12 (silica gel, 6% methanol in dichloromethane).

Analysis: calculated for C₃₄H₃₉Cl₂N₃O₅ · 0.5 H₂O C 62.93; H 6.21; N 6.48; Found C 62.86; H 6.19; N 6.30.

25

Example 3A

3.3A.1 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl-3-yl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide hydrochloride

30

1-[2-[3-(3,4-Dichloro-phenyl-3-yl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide (4.13 g, 6.45 mmol) was dissolved in dichloromethane (20 mL) and treated with a solution of dichloromethane saturated with HCl(g) (20 mL). The solution was allowed to stir for 1 h. The solution was concentrated *in vacuo* to obtain a residue. The residue was

35

dried under high vacuum at 56°C for 18 h to give the title compound:

mp=175-185°C (slow dec. to glass)

- 5 Analysis: calculated for $C_{34}H_{40}Cl_3N_3O_5$ C 60.32; H 5.95; N 6.21; Found C 60.09; H 6.32; N 6.11.

Example 4

10 Synthesis of 1-(2-[3-(3,4-dichloro-phenyl)-1-[2-(2-methoxy-phenyl)-acetyl]-pyrrolidin-3-yl]-ethyl)-4-phenyl-piperidine-4-carboxylic acid amide

4.1 Synthesis of [3-(3,4-dichloro-phenyl)-1-(2-methoxy-benzoyl)-3-(2-hydroxy-ethyl)-pyrrolidine
15 (No.027F103)

3-(3,4-Dichloro-phenyl)-3-(2-hydroxy-ethyl)-pyrrolidine, (218 mg, 0.83 mmol) was dissolved in
20 dichloromethane at -78°C and treated with 4-methylmorpholine (0.19 mL, 1.73 mmol, 2 eq.) and 2-methoxybenzoyl chloride (155 mg, 0.84 mmol, 1 eq.) in dichloromethane (3 x 1 mL). The solution was allowed to warm to 0°C and stir for 4.5 hours. The solution was washed with 1N HCl and 5% sodium
25 bicarbonate and the organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (30 g) with a gradient of 50% ethyl acetate in hexane to 6% methanol in dichloromethane to give 202 mg (60%) of the title compound.

30

4.2 Synthesis of 2-[3-(3,4-dichloro-phenyl)-1-[2-(2-methoxy-phenyl)-acetyl]-pyrrolidin-3-yl]-ethyl-methanesulfonate (No.027F104)

35 3-(3,4-Dichloro-phenyl)-1-(2-methoxy-benzoyl)-3-(2-hydroxy-ethyl)-pyrrolidine (No.027F103) (200 mg, 0.49 mmol) was dissolved in dichloromethane (5 mL) and diisopropylethylamine (0.17 mL, 0.976 mmol, 2 eq.) and

-106-

methanesulfonyl chloride (0.050 mL, 0.646 mmol, 1.3 eq.) were added dropwise at 0°C. The solution was allowed to stir for 30 minutes at 0°C. The solution was diluted with
5 dichloromethane and washed with 1 N HCl and 5% sodium bicarbonate. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (25 g) with a gradient from 50% ethyl acetate in hexane to 6% methanol in
10 dichloromethane to give 210 mg (88%) of the title compound.

4.3 Synthesis of 1-(2-[3-(3,4-dichloro-phenyl)-1-[2-(2-methoxy-phenyl)-acetyl]-pyrrolidin-3-yl]-ethyl)-4-phenyl-piperidine-4-carboxylic acid amide
15 (No.027F104)

2-[3-(3,4-Dichloro-phenyl)-1-(2-methoxy-benzoyl)-pyrrolidin-3-yl] ethyl methanesulfonate (No.027F104) (210 mg, 0.43 mmol), was dissolved in THF (4 mL) and 4-phenyl-
20 piperidine-4-carboxylic acid amide hydrochloride (105 mg, 0.44 mmol), sodium bicarbonate (75 mg, 0.89 mmol), and water (1 mL) , were added and the solution was heated at reflux for 22 hours. The solution was concentrated *in vacuo* and the aqueous phase was extracted with dichloromethane.
25 The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (30 g) with a gradient from ethyl acetate to 10% methanol in dichloromethane to give 205 mg (80%) of the title compound.
30 Analysis: calculated for $C_{33}H_{37}Cl_2N_3O_3 \cdot 0.5 H_2O$ C 65.47; H 6.16; N 6.94. Found C 65.86; H 6.43; N 7.02.

Example 5

5 Synthesis of 1-(2-[3-(3,4-dichloro-phenyl)-1-(2,6-
 dimethoxy-benzoyl-pyrrolidin-3-yl]-ethyl)-4-phenyl-
 piperidine-4-carboxylic acid amide

10 5.1 Synthesis of [3-(3,4-dichloro-phenyl)-1-(2,6-
 dimethoxy-benzoyl)-3-(2-hydroxy-ethyl)-pyrrolidine
 (No.027F130)

3-(3,4-Dichloro-phenyl)-3-(2-hydroxy-ethyl)-pyrrolidine
(2 g, 7.695 mmol) was dissolved in dichloromethane at
-78°C and treated with 4-methylmorpholine (1.8 mL, 16.4
15 mmol, 2.1 eq.) and 2,6-dimethoxy-benzoyl chloride (1.55 g,
7.73 mmol) in dichloromethane (20 mL). The solution was
allowed to warm to 0°C and stirred for 1.5 hours. The
solution was washed with 1N HCl and 5% sodium bicarbonate
and the organic phase was dried over magnesium sulfate,
20 filtered, and concentrated *in vacuo*. The residue was
chromatographed on silica gel (200 g) with a gradient of
50% ethyl acetate in hexane to 6% methanol in
dichloromethane to give 2.434 g (75%) of the title
compound.

25 5.2 Synthesis of 2-[3-(3,4-dichloro-phenyl)-1-(2,6-
 dimethoxybenzoyl)-pyrrolidin-3-yl]-ethyl-
 methanesulfonate (No.027F130)

30 3-(3,4-Dichloro-phenyl)-1-(2,6-dimethoxy-benzoyl)-3-(2-
hydroxy-ethyl)-pyrrolidine (2.434 g, 5.74 mmol), was
dissolved in dichloromethane (30 mL) and treated with N,N-
diisopropylethylamine (2.1 mL, 12.06 mmol, 2.1 eq.) and
methanesulfonyl chloride (0.53 mL, 6.85 mmol, 1.2 eq.) at
35 0°C for 1 hour. The solution was washed with 1 N HCl, and
5% sodium bicarbonate. The organic phase was dried over
magnesium sulfate, filtered, and concentrated *in vacuo*. The
residue was chromatographed on silica gel (150 g) with a

gradient of 50% ethyl acetate in hexane to 6% methanol in dichloromethane to give 2.8041 g (97%) of the title compound.

5

5.3 Synthesis of 1-(2-[3-(3,4-dichloro-phenyl)-1-(2,6-dimethoxy-benzoyl-pyrrolidin-3-yl)-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide (No.027F131)

10 2-[3-(3,4-Dichloro-phenyl)-1-(2,6-dimethoxybenzoyl)-pyrrolidin-3-yl] ethyl methanesulfonate (2.0 g, 3.98 mmol) was dissolved in THF (40 mL) and 4-phenyl-piperidine-4-carboxylic acid amide hydrochloride (1 g, 4.16 mmol), water (10 mL) , and potassium carbonate (1.2 g, 8.68 mmol) were
15 added and the solution was heated at reflux for 18 hours. The solution was concentrated *in vacuo*. The aqueous phase was extracted with dichloromethane three times and the organic phase was washed with water, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue
20 was chromatographed on silica gel (150 g) with a gradient from ethyl acetate to 10% methanol in dichloromethane to give 1.2515 g (52%) of a residue. CI/MS (m/e) 610 (M+H) for $C_{33}H_{37}Cl_2N_3O_4$.

25 The residue was dissolved in dichloromethane (5 mL) and filtered dropwise into a saturated ether/HCl solution. The slurry was concentrated *in vacuo* and the residue was dried under high vacuum at 55°C to give 1.04 g (78%) of the title compound.

30 Analysis: calculated for $C_{33}H_{37}Cl_2N_3O_4 \cdot HCl$ C 61.26; H 5.92; N 6.49. Found C 61.19; H 6.22; N 6.57.

Example 5A

5 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl-3-yl)-1-(2,6-dimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide hydrochloride

10 5A.1 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl-3-yl)-1-(2,6-dimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide hydrochloride

15 1-[2-[3-(3,4-Dichloro-phenyl-3-yl)-1-(2,6-dimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide (1.8 mmol) was dissolved in dichloromethane (20 mL) and treated with a solution of dichloromethane saturated with HCl(g) (20 mL). The solution was allowed to stir for 1 h. The solution was concentrated *in vacuo* to obtain a residue. The residue was
20 dried under high vacuum at 56°C for 18 h to give the title compound.

25 Analysis: calculated for $C_{33}H_{38}Cl_2N_3O_4$ C 61.26; H 5.92; N 6.49; Found C 61.18; H 6.22; N 6.57.

Example 6

30 Synthesis of 2-[(2-[1-benzoyl-3-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carbonyl)-amino]-pentanedioic acid dimethyl ester

35 6.1 Synthesis of 1-*tert*-butyloxycarbonyl-4-phenyl-piperidine-4-carboxylic acid methyl ester
(No.03F169)

1-*tert*-Butyloxycarbonyl-4-phenyl-piperidine-4-carboxylic acid (0.9162 g, 3 mmol) was allowed to react with methyl

iodide (1.87 mL, 30 mmol, 10 eq.) in the presence of N,N-diisopropylethylamine (2.61 mL, 15 mmol, 5 eq.) in acetonitrile (30 mL) at 20°C for 16 hours. The solution
5 was diluted with ethyl acetate and washed with 1 N HCl, saturated sodium bicarbonate and saturated sodium chloride. The organic phase was dried over magnesium sulfate and the solvent was concentrated *in vacuo* to give 0.935 g (98%) of the title compound.

10

6.2 Synthesis of 4-phenyl-piperidine-4-acid methyl ester hydrochloride (No.03F170)

1-*tert*-Butyloxycarbonyl-4-phenyl-piperidine-4-acid methyl
15 ester (0.9345 g, 2.93 mmol) was allowed to stir in 4 N HCl in dioxane (10 mL) at 20°C for 45 minutes. The solution was concentrated *in vacuo* and the residue was dried *in vacuo* to give 0.7143 g (95%) of the title compound.

20 6.3 Synthesis of 1-[2-[1-benzoyl-3-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid methyl ester (003F171)

4-Phenyl-piperidine-4-carboxylic acid methyl ester
25 hydrochloride (0.4143 g, 1.62 mmol) and 2-[1-benzoyl-3-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate (0.7165 g, 1.62 mmol) were dissolved in THF/H₂O (20 mL /4 mL) and treated with sodium bicarbonate (0.2592 g, 3.24 mmol) at reflux for 16 hours. The solution
30 was diluted with ethyl acetate and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel with 1% methanol in dichloromethane to give
35 0.2850 g (31%) of the title compound.

6.4 Synthesis of 1-[2-[1-benzoyl-3-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid (003F172)

5
1- [2-[1-Benzoyl-3-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid methyl ester (0.2850 g, 0.5 mmol) was dissolved in ethanol (10 mL) and treated with 1 M sodium hydroxide (5 mL, 5 mmol) at
10 20°C for 2 hours. The aqueous phase was washed with ethyl acetate. The aqueous phase was acidified with 1 N hydrochloric acid, and then extracted with ethyl acetate. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 0.117 g (43%) of
15 the title compound.

6.5 Synthesis of 2-[(2-[1-benzoyl-3-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethyl)-4-phenyl-piperidine-4-carboxyl]-amino]-pentanedioic acid dimethyl ester (003F175)

20
A mixture of 1-[2-[1-benzoyl-3-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid (49 mg, 0.11 mmol, 1.1 eq.), L-glutamic acid dimethyl
25 ester hydrochloride (0.0260 g, 0.1 mmol), EDC (0.0236 g, 0.12 mmol, 1.2 eq.), HOBT (0.0180 g, 0.12 mmol, 1.2 eq.), and N,N-diisopropylethylamine (0.03 mL, 0.12 mmol, 1.2 eq.) were dissolved in dichloromethane (2 mL) and stirred 16 hours at 20°C. The solution was diluted with ethyl acetate
30 and washed with 1 N hydrochloric acid, saturated sodium bicarbonate, and saturated sodium chloride. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel with 5% methanol in dichloromethane to give 63
35 mg (81%) of the title compound.

Analysis: calculated for $C_{38}H_{43}Cl_2N_3O_6$ C 64.40; H 6.11; N 5.93. Found C 64.07; H 6.28; N 5.87.

Example 7

5 Synthesis of 2-[(1-(2-[1-benzoyl-3-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethyl)-4-phenyl-piperidine-4-carboxyl)-amino]-3-hydroxy butyric acid methyl ester (003F176).

7.1 Synthesis of 2-[(1-(2-[1-benzoyl-3-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethyl)-4-phenyl-piperidine-4-carboxyl)-amino]-3-hydroxybutyric acid methyl ester (003F176).

10

1-[2-[1-Benzoyl-3-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid (61 mg, 0.1 mmol), L-threonine methyl ester hydrochloride (0.0187 g, 0.11 mmol, 1.1 eq.), EDC (0.0216 g, 0.11 mmol, 1.1 eq.), HOBT (0.0165 g, 0.11 mmol, 1.1 eq.), and N,N-diisopropylethylamine (0.0257 mL, 0.11 mmol, 1.1 eq.) were dissolved in dichloromethane (2 mL) and stirred 16 hours at 20°C. The solution was diluted with ethyl acetate and washed with 1 N hydrochloric acid, saturated sodium bicarbonate, and saturated sodium chloride. The organic phase was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was chromatographed on silica gel with 5% methanol in dichloromethane to give 34.2 mg (51%) of the title compound.

25

Analysis: calculated for C₃₆H₄₁Cl₂N₃O₅ C 64.86; H 6.20; N 6.30. Found C 64.62; H 6.49; N 6.42.

30

Example 8

Synthesis of 1-[2-[1-benzoyl-3-naphthyl-2-yl-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide.

35 8.1 Synthesis of 3-cyano-3-(2-naphthyl)-pentanedioic acid diethyl ester (03F106).

2-Naphthylacetonitrile (1.6721 g, 10 mmol) in THF (80 mL) at -78°C was treated with sodium bis-(trimethylsilyl)amide (20 mL, 1 M in THF; 20 mmol, 2 eq.).

5 The solution was allowed to warm to 20°C and stir for 2 hours. The solution was cooled to -78°C and ethyl bromoacetate (2.2 mL, 20 mmol, 2 eq.) was added. The solution was allowed to warm to 20°C and stir 16 hours. The solution was diluted with dichloromethane and washed
10 with water. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel with a gradient from 5% ethyl acetate in hexane to 20% ethyl acetate in hexane to give 3.2124 g (95%) of the title compound.

15

8.2 Synthesis of [3-naphthalen-2-yl-5-oxo-pyrrolidin-3-yl]-acetic acid ethyl ester (003F115).

3-Cyano-3-(2-naphthyl-pentanedioic acid diethyl ester
20 (3.2124 g, 9.47 mmol) was hydrogenated at 40 psi over Raney nickel (10 g) in ethanol (60 mL) and ammonium hydroxide (25 mL) for 8 hours. The slurry was filtered and the filtrate was concentrated *in vacuo*. The residue was
25 chromatographed on silica gel with a gradient from 30% ethyl acetate in hexane to 2% methanol in dichloromethane to give 1.0337 g (68%) of the title compound.

8.3 Synthesis of 3-(2-naphthalen-2-yl-pyrrolidin-3-yl-ethanol (003F122).

30

3-(2-Naphthalen-2-yl-5-oxo-pyrrolidin-3-yl)-acetic acid ethyl ester (1.2636 g, 4.25 mmol) in THF (20 mL) was added slowly to a solution of LAH (0.6451 g, 17 mmol) in THF (20 mL) at room temperature. The slurry was heated at reflux
35 for 12 hours and additional LAH (0.3225 g, 8.5 mmol) was added and then heated at reflux for an additional 8 hours. The slurry was treated dropwise with 0.98 mL of H₂O, 0.98 mL of 15% sodium hydroxide, and 2.94 mL of H₂O. The slurry

was dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 0.9145 g (89%) of the title compound.

5

8.4 Synthesis of 1-benzoyl-3-(2-hydroxyethyl)-3-(2-naphthyl)pyrrolidine (003F129)

3-(2-Naphthylen-2-yl-pyrrolidin-3-yl)-ethanol (003F122)
10 (0.1207 g, 0.5 mmol crude) was dissolved in dichloromethane and cooled to 0°C. Benzoyl chloride (0.06 mL, 0.5 mmol, 1 eq.) and N,N-diisopropylethylamine (0.09 mL, 0.5 mmol, 1 eq.) were added at 0°C. The solution was stirred at 0°C for 4 hours and then diluted with ethyl acetate and washed with
15 1N HCl, saturated sodium bicarbonate, and saturated sodium chloride. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel with a gradient from 35% ethyl acetate in hexane to 4% methanol in CHCl₃ to give
20 0.1061 g (61%) of the title compound.

8.5 Synthesis of 2-[1-benzoyl-3-naphthylen-2-yl-pyrrolidin-3-yl]-ethyl-methanesulfonate (003F134).

25 1-Benzoyl-3-(2-hydroxyethyl)-3-(2-naphthyl)pyrrolidine 003F129 (1.0501 g, 3.04 mmol) in dichloromethane (30 mL) was cooled to 0°C, and treated with N,N-diisopropylethylamine (0.93 mL, 3.95 mmol, 1.3 eq.) and methanesulfonyl chloride (0.28 mL, 3.65 mmol, 1.2 eq.).
30 The solution was allowed to stir at 0°C for 2 hours and more N,N-diisopropylethylamine (0.93 mL, 3.95 mmol, 1.3 eq.) and methanesulfonyl chloride (0.28 mL, 3.65 mmol, 1.3 eq.) was added and the solution was allowed to stir for an additional 2 hours at 0°C. The solution was concentrated *in*
35 *vacuo* and the residue was chromatographed on silica gel with 1% methanol in dichloromethane to give 1.297 g (97%) of the title compound.

8.6 Synthesis of 1-[2-[1-benzoyl-3-naphthyl-2-yl-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide (003F136)

5

2-[1-Benzoyl-3-naphthyl-2-yl-pyrrolidin-3-yl]-ethyl methanesulfonate (003F134), (1.1363 g, 2.58 mmol), 4-phenyl-piperidine-4-carboxylic acid amide hydrochloride (0.6846 g, 2.84 mmol, 1.1 eq.), sodium bicarbonate (0.4335 g, 5.16 mmol, 2 eq.) in THF/H₂O (25 mL/5 mL) was heated at reflux for 16 hours. The solution was concentrated *in vacuo* and the aqueous phase was extracted with dichloromethane. The organic phase was washed with water, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel with a gradient from 3% methanol in dichloromethane to 5% methanol in dichloromethane to give 0.8325 g (61%) of the title compound.

20 Analysis: calculated for C₃₅H₃₇N₃O₂ · H₂O C 76.48; H 7.15; N 7.64. Found C 76.10; H 7.13; N 7.71.

Example 9

25 Synthesis of 8-[2-[3-(3,4-dichloro-phenyl)-1-(2,6-dimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-1-phenyl-1,3,8-triaza-spiro[4.5]decane-4-one (027F145).

30 9.1 Synthesis of 8-[2-[3-(3,4-dichloro-phenyl)-1-(2,6-dimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-1-phenyl-1,3,8-triaza-spiro[4.5]decane-4-one (027F145).

35 2-[1-(2,6-Dimethoxy-benzoyl)-3-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethyl methanesulfonate (200 mg, 0.398 mmol), and 1-phenyl-1,3,8-triaza-spiro[4.5]decane-4-one (100 mg, 0.432 mmol) were dissolved in THF/H₂O (4 mL /1 mL) and treated with potassium carbonate (110 mg, 0.796 mmol, 2

- eq.) at reflux for 22 hours. The solution was concentrated *in vacuo* and the aqueous phase was extracted (3x) with dichloromethane. The organic phase was dried over
- 5 magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (40 g) with a gradient from ethyl acetate to 10% methanol in dichloromethane to give 130 mg (51%) of the title compound.
- 10 Exact mass (Cl): calculated for $C_{34}H_{39}Cl_2N_4O_4$ (M+H): 637.2348. Found 637.2322.

Example 10

- 15 Synthesis of 8-[2-[3-(3,4-dichloro-phenyl)-1-benzoyl-pyrrolidin-3-yl]-ethyl]-1-phenyl-1,3,8-triaza-spiro[4.5]-decane-4-one (027F60).
- 10.1 Synthesis of 2-[1-benzoyl-3-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate (027F60a).
- 20

- 1-Benzoyl-3-(2-hydroxyethyl)-3-(3,4-dichlorophenyl) pyrrolidine (350 mg, 0.962 mmol) was dissolved in dichloromethane (6 mL) at 0°C and N,N-diisopropylethylamine
- 25 (0.25 mL, 1.44 mmol, 1.5 eq.) and methanesulfonyl chloride (0.090 mL, 1.16 mmol, 1.2 eq.) were added. The solution was allowed to stir for 2 hours. Methanesulfonyl chloride (0.015 mL, 0.19 mmol, 0.2 eq.) was added and the solution was allowed to stir an additional 30 minutes. The solution
- 30 was diluted with dichloromethane and washed with 1N HCl and 5% sodium bicarbonate. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (40g) with 2% methanol in dichloromethane to give 427 mg (99%) of the
- 35 title compound.

10.2 Synthesis of 8-[2-[3-(3,4-dichloro-phenyl)-1-(benzoyl)-pyrrolidin-3-yl]-ethyl]-1-phenyl-1,3,8-triaza-spiro[4.5]-decane-4-one (027F60b).

5

2-[1-Benzoyl-3-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate (427 mg, 0.962 mmol) (027F60a), was dissolved in THF (6 mL) and 1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one (270 mg, 1.167 mmol, 1.2 eq.), water 10 (1.5 mL) and sodium bicarbonate (150 mg, 1.79 mmol, 1.86 eq.) were added. The slurry was heated at reflux for 21 hours and then concentrated *in vacuo*. The aqueous phase was extracted with dichloromethane. The organic phase was washed with water, dried over magnesium sulfate, filtered, 15 and concentrated *in vacuo*. The residue was chromatographed on silica gel (50 g) with a gradient from ethyl acetate to 10% methanol in dichloromethane to give 354 mg (64%).

Analysis: calculated for $C_{32}H_{34}Cl_2N_4O_2 \cdot H_2O$ C 64.60; H 6.10; N 9.42. Found C 64.79; H 6.04; N 9.27.

EXAMPLE 11

25 Synthesis of 1-[2-[1-benzyl-3-(3,4-dichloro-phenyl)-5-oxo-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide

11.1 Synthesis of 2-(3,4-dichloro-phenyl)-4-(tetrahydro-pyran-2-yl-oxy)-butyronitrile

30

Sodium hydride (1.42 g, 59.2 mmol) in THF (25 mL) was treated with 3,4-dichlorophenylacetonitrile (10 g, 53.75 mmol) in THF (60 mL) at -78°C and then the slurry was allowed to warm to 20°C and stir for 2.5 hours. The 35 solution was cooled to 0°C and 2-(2-bromo-ethoxy)-tetrahydro-pyran in THF (25 mL) was added dropwise. The solution was allowed to warm to 20°C and stir for 16 hours. The solution was poured into saturated ammonium chloride

and extracted with diethyl ether. The organic phase was extracted with water and brine and the organic phase was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was chromatographed on silica gel (500 g) with a gradient from 5% ethyl acetate in hexane to 20% ethyl acetate in hexane to give 12.134 g (72%) of the title compound.

10 11.2 Synthesis of 3 cyano-3-(3,4-dichloro-phenyl)-5-(tetrahydro-pyran-2-yloxy) pentanoic acid ethyl ester (027F32-33).

2-(3,4-dichloro-phenyl)-4-(tetrahydro-pyran-2-yloxy)-butyronitrile (10.8669 g, 34.62 mmol) was dissolved in THF (20 mL) at -78°C and treated dropwise with LDA (27.2 mL, 40.8 mmol, 1.18 eq.) over 30 minutes. The solution was allowed to stir for 1.25 hour. Ethyl bromoacetate (4.2 mL, 37.87 mmol, 1.09 eq.) was added dropwise at -78°C and the solution was allowed to warm to 20°C and stir for 4 hours. The solution was partitioned between ammonium chloride and diethyl ether. The organic solution was extracted with water and brine and the organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (400 g) with a gradient from 20% ethyl acetate in hexane to 30% ethyl acetate in hexane to give 9.6243 g (69.5%) of the title compound.

30 11.3 Synthesis of 4-(3,4-dichloro-phenyl)-4-(tetrahydro-pyran-2-yloxy)ethyl-pyrrolidin-2-one (027F34).

3-Cyano-3-(3,4-dichloro-phenyl)-5-(tetrahydro-pyran-2-yloxy) pentanoic acid ethyl ester (027F32a) (9.5 g, 23.76 mmol) was dissolved in ethanol/ammonium hydroxide (190 mL /38 mL) and hydrogenated in a Parr shaker at 45 psi for 7 hours over Raney nickel (30 g). The slurry was filtered and the filtrate was concentrated *in vacuo*. The residue was

chromatographed on silica gel (30 g) with a gradient from 30% ethyl acetate in hexane to 10% methanol in dichloromethane to give 6.85 g (81%) of the title compound.

5

11.4 Synthesis of 1-benzyl-4-(3,4-dichloro-phenyl)-4-[2-(tetrahydro-pyran-2-yloxy)ethyl]-pyrrolidin-2-one
(027F43).

10 4-(3,4-Dichloro-phenyl)-4-(tetrahydro-pyran-2-yloxy)ethyl-pyrrolidin-2-one (027F34) (1 g, 2.79 mmol) was dissolved in THF (10 mL) and treated with sodium hydride (80 mg, 1.2 eq.) and benzyl bromide (0.7 mL, 5.89 mmol) at 20°C. The solution was allowed to stir 7.5 hours. The
15 slurry was partitioned between diethyl ether and ammonium chloride and the solution was washed with water and brine. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (100 g) with 50% ethyl
20 acetate in hexane to give 1.194 g (99%) of the title compound.

11.5 Synthesis of 1-benzyl-4-(3,4dichloro-phenyl)-4-(2-hydroxy-ethyl-pyrrolidin-2-one (027F44a).

25

1-Benzyl-4-(3,4-dichloro-phenyl)-4-[2-(tetrahydro-pyran-2-yloxy)ethyl]-pyrrolidin-2-one (027F43) (1.0 g, 2.79 mmol) was dissolved in methanol (6 mL) and treated with p-toluenesulfonic acid (200 mg) at room temperature for 5
30 hours. The solution was concentrated *in vacuo* and the residue was dissolved in dichloromethane and washed with 5% sodium bicarbonate and water. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified on silica gel (100 g) with a
35 gradient from 50% ethyl acetate in hexane to 10% methanol in dichloromethane to give 779 mg (77%) of the title compound.

11.6 Synthesis of 2-[4-benzyl-3-(3,4-dichloro-phenyl)-5-oxo-pyrrolidin-3-yl]-ethyl methanesulfonate (027F44b).

5

1-Benzyl-4-(3,4-dichloro-phenyl)-4-(2-hydroxy-ethyl-pyrrolidin-2-one (027F44a) (779 mg, 2.14 mmol) was dissolved in dichloromethane (10 mL) and treated with N,N-diisopropylethylamine (0.5 mL, 2.87 mmol, 1.34 eq.) and
10 methanesulfonyl chloride (0.2 mL, 2.58 mmol, 1.2 eq.) at 0°C for 2 hours. The solution was washed with 1N HCl, 5% sodium bicarbonate, and water, and the organic phase was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was chromatographed on silica gel (100g)
15 with a gradient from 50% ethyl acetate in hexane to ethyl acetate to give 815 mg (86%) of the title compound.

11.7 Synthesis of 1-[2-[1-benzyl-3-(3,4-dichloro-phenyl)-5-oxo-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide (027F44c).

20

2-[4-Benzyl-3-(3,4-dichloro-phenyl)-5-oxo-pyrrolidin-3-yl]-ethyl methanesulfonate (027F44b) (815 mg, 1.84 mmol) was dissolved in THF/water (15ml/4ml) and 4-phenyl-
25 piperidine-4-carboxylic acid amide hydrochloride (520 mg, 2.16 mmol, 1.17 eq.) and sodium bicarbonate (320 mg, 3.8 mmol, 2.1 eq) were added. The solution was heated at reflux for 16 hours. The solvents were concentrated *in vacuo*. The aqueous phase was extracted with dichloromethane
30 and the organic phase was washed with water. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (100 g) with 10% methanol in dichloromethane to give 389 mg (38%) of the title compound.

35

Exact mass (Cl): calculated for C₃₁H₃₄Cl₂N₃O₂ (M+H)
550.2028. Found 550.2018.

EXAMPLE 12

5 Synthesis of 1-[1-benzyl-3-naphthalen-2-yl-5-oxo-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide (003F112-113)

10 12.1 Synthesis of 2-(2-naphthyl)-4-(tetrahydro-pyran-2-yloxy)-butyronitrile (003F112)

2-Naphthylacetonitrile (3.3442 g, 20 mmol) in THF (50 mL) was added to sodium hydride (0.528 g, 22 mmol, 1.1 eq.) in THF (50 mL) at -78°C under nitrogen. The slurry was allowed to warm to 20°C and stir for 2 hours. The slurry
15 was cooled to 0°C and 2-(2-bromo-ethoxy)-tetrahydro-pyran (4.1786 g, 20 mmol, 1 eq.) was added. The solution was allowed to stir at 20°C for 16 hours and then diluted with dichloromethane and washed with water. The organic phase was dried over magnesium sulfate, filtered and concentrated
20 *in vacuo*. The residue was chromatographed on silica gel with a gradient from 5% ethyl acetate in hexane to ethyl acetate to give 1.9774 g (66%) of the title compound.

25 12.2 Synthesis of 3-cyano-3-naphthalen-2-yl-5-(tetrahydro-pyran-2-yloxy)-pentanoic acid ethyl ester (003F143).

2-(2-Naphthyl)-4-(tetrahydro-pyran-2-yloxy)-butyronitrile (003F112) (1.9 g, 6.45 mmol) in THF (60 mL)
30 was cooled to -78°C and treated dropwise with LDA (1.5 M, 5.2 mL, 7.75 mmol, 1.2 eq.) and allowed to stir for 1 hour. Ethyl bromoacetate (0.86 mL, 7.75 mmol, 1.2 eq.) was added dropwise and the solution was allowed to warm to 20°C and stir for 18 hours. The solution was partitioned between
35 saturated aqueous ammonium chloride solution and ethyl acetate. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel with a gradient from 20%

ethyl acetate in hexane to 50% ethyl acetate in hexane to give 1.474 g (39%) of the title compound.

5 12.3 Synthesis of 4-naphthalen-2-yl-4-[2(tetrahydro-pyran-2-yloxy)-ethyl]-pyrrolidin-2-one (003F144).

3-Cyano-3-naphthalen-2-yl-5-(tetrahydro-pyran-2-yloxy)-pentanoic acid ethyl ester (003F143) (1.6154 g, 4.23 mmol)
10 was hydrogenated at 40 psi over Raney nickel (10g) for 16 hours. The slurry was filtered and the filtrate was concentrated *in vacuo*. The residue was chromatographed on silica gel with a gradient from 50% ethyl acetate in hexane to 5% methanol in dichloromethane to give 0.8305 g (83%) of
15 the title compound.

12.4 Synthesis of 1-benzyl-4-naphthalen-2-yl-4-[2-(tetrahydro-pyran-2-yloxy)-ethyl]pyrrolidin-2-one (003F145).

20

Sodium hydride (0.07 g, 2.94 mmol, 1.25 eq.) was added slowly to a solution of 4-naphthalen-2-yl-4-[2(tetrahydro-pyran-2-yloxy)-ethyl]-pyrrolidin-2-one (003F144) (0.81 g, 2.39 mmol). The solution was treated with benzyl bromide
25 (0.6 mL, 4.9 mmol, 2 eq.) at 20°C for 7 hours. The solution was partitioned between saturated aqueous ammonium chloride and ethyl acetate. The organic phase was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was chromatographed on silica gel with 50%
30 ethyl acetate in hexane to give 1.1620 g (92%) of the title compound.

12.5 Synthesis of 1-benzyl-4-(2-hydroxy-ethyl)-4-naphthalene-2-yl-pyrrolidin-2-one (003F146).

35

1-Benzyl-4-naphthalen-2-yl-4-[2-(tetrahydro-pyran-2-yloxy)-ethyl]pyrrolidin-2-one (003F145) (1.1620g, 2.71 mmol) was dissolved in methanol (2.7 mL) and treated with

p-toluenesulfonic acid (0.0515 g, 0.27 mmol, 0.1 eq.). The solution was allowed to stir at 20°C for 4 hours. The residue was chromatographed on silica gel with a gradient from 50% ethyl acetate in hexane to 5% methanol in dichloromethane to give the 0.6161 g (66%) of the title compound.

12.6 Synthesis of 2-[1-benzyl-3-naphthalene-2-yl-5-oxo-pyrrolidin-3-yl] ethyl methanesulfonate (003F147).

1-Benzyl-4-(2-hydroxyethyl)-4-naphthalene-2-yl-pyrrolidin-2-one (003F146) (0.6161 g, 1.78 mmol) in dichloromethane (17 mL) at 0°C was treated with N,N-diisopropylethylamine (0.84 mL, 3.56 mmol, 2 eq.) and methanesulfonyl chloride (0.27 mL, 3.56 mmol, 2 eq.). The solution was allowed to stir at 0°C for 2 hours. The solution was concentrated and the residue was chromatographed on silica gel with 1% methanol in dichloromethane to give 0.7219 g (95%) of the title compound.

12.7 Synthesis of 1[2-(1-benzyl)-3-naphthalen-2-yl-5-oxo-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide (003F148).

2-[1-Benzyl-3-naphthalene-2-yl-5-oxo-pyrrolidin-3-yl]-ethyl-methanesulfonate (003F147) (0.5061 g, 1.19 mmol) was dissolved in THF/H₂O (12 mL /2 mL) and treated with 4-phenyl-piperidine-4-carboxylic acid amide hydrochloride (0.3155 g, 1.31 mmol, 1.1 eq.) and sodium bicarbonate (0.1999 g, 2.38 mmol) at reflux for 18 hours. The aqueous phase was extracted with dichloromethane and the organic phases were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was chromatographed on silica gel with 5% methanol in dichloromethane to give 0.5060 g (80%) of the title compound.

-124-

Exact mass (CI): calculated for $C_{35}H_{38}N_3O_2$ (M+H): 532.2964.
Found 532.2981.

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Example 13

5 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(2-methoxy-
 benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-
 carboxylic acid amide

10 13.1 Synthesis of [3-(3,4-dichloro-phenyl)-1-(2-methoxy-
 benzoyl)-3-(2-hydroxy-ethyl)-pyrrolidine
 (No.027F099)

 3-(3,4-Dichloro-phenyl)-3-(2-hydroxy-ethyl)-pyrrolidine
 (200 mg, 0.76 mmol) was dissolved in dichloromethane (5 mL)
 at -78°C and treated with 4-methylmorpholine (0.17 mL,
15 1.55 mmol, 2 eq.) and 2-methoxy-benzoyl chloride (0.11 mL,
 0.74 mmol). The solution was allowed to warm to 0°C and
 stir for 1 hour. The solution was washed with 1N HCl and
 5% sodium bicarbonate and the organic phase was dried over
 magnesium sulfate, filtered, and concentrated *in vacuo*. The
20 residue was chromatographed on silica gel (30 g) with a
 gradient of 50% ethyl acetate in hexane to 3% methanol in
 dichloromethane to give 268 mg (90%) of the title compound.

25 13.2 Synthesis of 2-[3-(3,4-dichloro-phenyl)-1-(2-
 methoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-
 methanesulfonate (No.027F100)

 [3-(3,4-Dichloro-phenyl)-1-(2-methoxy-benzoyl)-3-(2-
 hydroxy-ethyl)-pyrrolidine (268 mg, 0.68 mmol) was
30 dissolved in dichloromethane (5 mL) and treated with N,N-
 diisopropylethylamine (0.24 mL, 1.38 mmol, 2 eq.) and
 methanesulfonyl chloride (65 mL, 0.84 mmol, 1.2 eq.) at 0°C
 for 1 hour. The solution was washed with 1 N HCl, and 5%
 sodium bicarbonate. The organic phase was dried over
35 magnesium sulfate, filtered, and concentrated *in vacuo*. The
 residue was chromatographed on silica gel (30g) with ethyl
 acetate to give 323 mg (99%) of the title compound.

13.3 Synthesis of 1-(2-[3-(3,4-dichloro-phenyl)-1-(2-methoxy-benzoyl)-pyrrolidin-3-yl]-ethyl)-4-phenyl-piperidine-4-carboxylic acid amide

5 (No. 027F131)

2-[3-(3,4-Dichloro-phenyl)-1-(2-methoxybenzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate (323 mg, 0.68 mmol) was dissolved in THF (4 mL) and 4-phenyl-piperidine-4-carboxylic acid amide hydrochloride (165 mg, 0.69 mmol),
10 water (1 mL), and sodium bicarbonate (105 mg, 1.25 mmol) were added and the solution was heated at reflux for 21 hours. The solution was concentrated *in vacuo*. The aqueous phase was extracted with dichloromethane (3X) and the
15 organic phase was washed with water, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (30g) with a gradient from ethyl acetate to 6% methanol in dichloromethane to give 280 mg (73%) of the title compound.

20

Exact mass (Cl): calculated for $C_{32}H_{36}Cl_2N_3O_3$ (M+H):
580.2134. Found 580.2143.

25

30

35

Example 20

5 Synthesis of (+)-1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide

10 20.2 Synthesis of ethyl-2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-acetate

2-[3-(3,4-Dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethanol (4.5 g, 9.9 mmol) was
15 dissolved in dichloromethane/pyridine (70 mL, 6/1). The solution was treated with acetic anhydride (1.04 mL, 11.02 mmol, 1.1 eq.) and 4-dimethylaminopyridine (50 mg, 0.41 mmol, 0.04 eq.). The solution was allowed to stir for 2 h at ambient temperature. The organics were concentrated *in vacuo* and the residue was dissolved in ethyl acetate and
20 washed with 1N HCl (2 X 200 mL), 5% NaHCO₃ (100 mL), brine (100 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was chromatographed on silica gel (300 g) with ethyl acetate to afford the title compound:
25 R_f=0.38 (silica gel, ethyl acetate).

Analysis: calculated for C₂₄H₂₇Cl₂NO₆ C 58.07; H 5.48; N 2.82; Found C 57.67; H 5.46; N 2.84.

30 20.3 Synthesis of (+)-ethyl-2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-acetate

Ethyl-2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-acetate (6.6 g, 13.31 mmol) was
35 dissolved in dichloromethane (100 mL) and treated with silica gel (32 g). The slurry was concentrated *in vacuo* and the residue was added to a 2 L three necked round-bottomed

flask. The residue was suspended in phosphate buffer (800 mL, 0.1 M, pH=7.5, the buffer was prepared with 11.5 g H₃PO₄ (85%) diluted to 1 L with deionized H₂O and then adjusting the pH with solid KOH pellets to 7.5). The slurry was treated with Lipase (13 g, EC 3.1.1.3, Type VII, from *Candida cylindracea*). The slurry was allowed to stir at ambient temperature for 84 h. The reaction was monitored by HPLC on a CHIRALPAK AD 25 cm X 0.46 cm column eluting with pentane/ethanol/methanol (80/15/5) with a flow rate of 1.0 mL/minute. An aliquot (50 mL) was extracted with ethyl acetate (1 mL) in a centrifuge tube. The solution was centrifuged for 10 minutes at 14000 cm⁻¹. The supernatant was removed and concentrated under a nitrogen stream. The residue was dissolved in dichloromethane (ca. 1 mL) and 5 mL was injected on the column for analysis. When the enantiomeric excess (ee) was satisfactory (>95% ee) for the (+) acetate the reaction was filtered. The filtrate was extracted with dichloromethane (8 X 500 mL). The solids were rinsed with dichloromethane (8 X 500 mL, the same portion was then used to extract the filtrate). The solids were placed in a chromatography column and eluted with 6% methanol in dichloromethane until all the alcohol and acetate was eluted. The combined organics were concentrated *in vacuo*, dissolved in dichloromethane, dried over MgSO₄, filtered and concentrated *in vacuo* to give a residue. The residue was chromatographed on silica gel (400 g), eluting with ethyl acetate until the acetate was off and then eluting with 6% methanol in dichloromethane until the alcohols were off to give the title compound: R_f=0.38 (silica gel, ethyl acetate).

Analysis: calculated for C₂₄H₂₇Cl₂NO₆·0.5 H₂O C 57.14; H 5.59; N 2.78; Found C 57.37; H 5.45; N 2.87.

HPLC determination of enantiomeric excess was 99%.

[α]_D²⁰ = +36.4°(c=0.894, CHCl₃).

20.4 Synthesis of (+)-2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethanol

5

(+)-Ethyl-2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-acetate (670 mg, 1.351 mmol, 99% ee) was dissolved in methanol (15 mL) and treated with LiOH (4.2 mL, 1N, 3.1 eq.) at ambient temperature for 3.5 h. The organics were concentrated *in vacuo*. The residue was dissolved in dichloromethane and washed with 1N HCl (50 mL), 5% NaHCO₃ (50 mL), dried over MgSO₄, filtered, and concentrated *in vacuo* to obtain a residue. The residue was dried under high vacuum for 18 h to give the title compound:
R_f=0.11 (silica gel, ethyl acetate).

20.5 Synthesis of (+)-2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate

20

Prepare by the method of example 3.2 using (+)-2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethanol (1.351 mmol) and methanesulfonyl chloride (0.14 mL, 1.81 mmol, 1.34 eq.) to obtain a residue. The residue was dried under high vacuum for 18 h to give the title compound:
R_f=0.27 (silica gel, ethyl acetate).

30 Synthesis of 4-phenyl-piperidine-4-carboxylic acid amide hydrochloride

20.6 Synthesis of 4-phenyl-piperidine-4-carboxylic acid hydrochloride

35

4-Cyano-4-phenylpiperidine hydrochloride (20.0 g, 89.8 mmol) and KOH (1.2 L, 3N, 3.6 mol, 40 eq.) were combined and heated at reflux for 15 h. The solution was cooled in

an ice bath and treated dropwise with conc. HCl until the pH=2. The white precipitate was collected and dried under high vacuum at 56°C for 15 h to give the title compound:

5 $R_f=0.2$ (silica gel, 85:10:5, chloroform:methanol:acetic acid).

Analysis: calculated for $C_{12}H_{16}ClNO_2$ C 59.63; H 6.67; N 5.79; Found C 58.19; H 6.52; N 5.72.

10

20.7 Synthesis of 1-tert-butoxycarbonyl-4-phenyl-piperidine-4-carboxylic acid

4-Phenyl-piperidine-4-carboxylic acid hydrochloride
15 (2.42 g, 10 mmol) was combined with di-tert-butyl dicarbonate (2.4 g, 11 mmol) in DMF (100 mL). N,N-diisopropylethylamine (1.91 mL, 11 mmol) was added to the mixture and the mixture was allowed to stir at ambient temperature for 30 h. The mixture was diluted with ethyl
20 acetate and extracted with 1N HCl. The organic phase was extracted with 1N NaOH (2 X 200 mL). The aqueous phase was cooled in an ice bath and treated with 1N HCl to pH=2. The aqueous phase was extracted with ethyl acetate. The organic phase was dried over $MgSO_4$, filtered, and
25 concentrated *in vacuo* to give a residue. The residue was dried under high vacuum to give the title compound:
 $R_f=0.48$ (silica gel, 6% methanol in dichloromethane, stains brown with ninhydrin).

30 Analysis: calculated for $C_{17}H_{23}NO_4$ C 66.86; H 7.59; N 4.59; Found C 66.56; H 7.72; N 4.52.

20.8 Synthesis of 1-tert-butoxycarbonyl-4-phenyl-piperidine-4-carboxylic acid amide

35

1-tert-Butoxycarbonyl-4-phenyl-piperidine-4-carboxylic acid (1.22 g, 4 mmol) was combined with THF (40 mL) and cooled to -10°C. Triethylamine (0.61 mL, 4.4 mmol, 1.1 eq.)

and isobutylchloroformate (0.57 mL, 4.4 mmol, 1.1 eq.) were added and the reaction was allowed to warm to ambient temperature and stir 15 h. The slurry was filtered and the solids were rinsed with THF. The filtrate was cooled to -10°C and sparged with NH₃(gas) for 0.5 h. The slurry was allowed to warm to 20°C and stir for 15 h. The slurry was filtered and the filtrate was diluted with ethyl acetate and washed with saturated NaHCO₃ (3X). The organic phase was dried over MgSO₄, filtered, and concentrated *in vacuo* to give a residue. The residue was recrystallized from diethyl ether to give the title compound:
R_f=0.48 (silica gel, 6% methanol in dichloromethane, stains blue with ninhydrin).

Analysis: calculated for C₁₇H₂₄N₂O₃ C 67.08; H 7.95; N 9.20; Found C 66.99; H 8.00; N 9.14. HPLC analysis R_t=30.16 min. using a Vydac C-18 column eluting with an acetonitrile:water (0.1% TFA) gradient (elution with CH₃CN/H₂O(0.1%TFA), flow rate = 1.0 mL/min., 10% CH₃CN for 10 minutes, 30% CH₃CN for 15 minutes, 40% CH₃CN for 15 minutes, 50% CH₃CN for 10 minutes, and then 100% CH₃CN).

20.9 Synthesis of 1-tert-butoxycarbonyl-4-phenyl-
25 piperidine-4-carboxylic acid amide

1-tert-Butoxycarbonyl-4-phenyl-piperidine-4-carboxylic acid (1.22 g, 4 mmol) was combined with dichloromethane (40 mL). N,N-diisopropylethylamine (0.77 mL, 4.4 mmol, 1.1 eq.), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) (0.8435 g, 4.4 mmol, 1.1 eq.), and 1-hydroxybenzotriazole hydrate (HOBT) (0.5946 g, 4.4 mmol, 1.1 eq.) were added. The mixture was allowed to stir at ambient temperature for 15 h. The solution was sparged with NH₃(gas) for 0.5 h and then allowed to stir at ambient temperature for 15 h. The mixture was filtered and the filtrate was concentrated *in vacuo* to give a residue. The residue was dissolved in ethyl acetate and extracted with

saturated NaHCO_3 (6X). The organic phase was dried over MgSO_4 , filtered, and concentrated *in vacuo* to give a residue. The residue was recrystallized from diethyl ether to give the title compound:
 $R_f=0.48$ (silica gel, 6% methanol in dichloromethane, stains blue with ninhydrin).

20.10 Synthesis of 4-phenyl-piperidine-4-carboxylic acid amide-hydrochloride

1-*tert*-Butoxycarbonyl-4-phenyl-piperidine-4-carboxylic acid amide (0.95 g, 3.12 mmol) was combined with HCl in dioxane (10 mL, 4N, 40 mmol, 13 eq.) at ambient temperature for 1 h. The solvent was concentrated *in vacuo* and ethyl acetate was added. The slurry was filtered and dried under high vacuum for 48 h to give the title compound:
HPLC analysis $R_t=5.56$ min. using a C-18 column eluting with a acetonitrile:water (0.1% TFA), flow rate = 1.0 mL/min., gradient (elution with $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (0.1% TFA) 10% CH_3CN for 10 minutes, 30% CH_3CN for 15 minutes, 40% CH_3CN for 15 minutes, 50% CH_3CN for 10 minutes, and then 100% CH_3CN).

Analysis: calculated for $\text{C}_{12}\text{H}_{17}\text{ClN}_2\text{O}$ C 59.87; H 7.12; N 11.64; Found C 59.82; H 7.00; N 11.52.

20.11 Synthesis of (+)-1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide

Prepare by the method of example 3.3 using (+)-2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate (1.351 mmol) and 4-phenyl-piperidine-4-carboxylic acid amide hydrochloride (480 mg, 1.99 mmol, 1.5 eq.) to obtain a residue. The residue was chromatographed on silica gel (70 g) packed with ethyl acetate, loaded with ethyl acetate,

and eluted with ethyl acetate, 6% methanol in dichloromethane, and then 10% methanol in dichloromethane to give the title compound:

- 5 HPLC determination of enantiomeric excess was 96.8%.
 R_t =13 minutes (with analytical column using a CHIRALPAK AD chiral HPLC column (25 cm X 0.46 cm) with 15% methanol in pentane and a flow rate of 1.0 mL/minute.

10

20A.1 Synthesis of (+)-1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide hydrochloride

15

- (+)-1-[2-[3-(3,4-Dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide (1.17 g, 96.8% ee, 1.828 mmol) was dissolved in dichloromethane (20 mL) and treated with a
20 solution of dichloromethane saturated with HCl(gas) (20 mL). The solution was allowed to stir for 1 h. The solution was concentrated *in vacuo* to obtain a residue. The residue was dried under high vacuum at 56°C for 18 h to afford the title compound:

- 25 mp=173-185°C (slow dec. to glass)
HPLC determination of enantiomeric excess was 96.8%.
 R_t =13 minutes (with analytical column using a CHIRALPAK AD chiral HPLC column (25 cm X 0.46 cm) with 15% methanol in pentane and a flow rate of 1.0 mL/minute.

30

Analysis: calculated for $C_{34}H_{39}Cl_2N_3O_5 \cdot 0.77 H_2O$ C 59.11; H 6.06; N 6.08; Found C 59.50; H 6.11; N 6.07.
 $[\alpha]^{20}_D = +13.2^\circ (c=0.851, CH_3OH)$.

35

Example 21

Chromatographic Resolution of (-)-1-[2-[3-(3,4-dichloro-

phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide

- 5 Chromatographic Resolution of (+) and (-)-1-[2-[3-(3,4-Dichloro-and phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide
- 10 A racemic mixture of 1-[2-[3-(3,4-Dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide hydrochloride (120 mg, 0.18 mmol) was resolved into two enantiomers on a CHIRALPAK AD chiral HPLC column (25 cm X 2 cm) using 15% methanol in pentane to give the title compound:
15 R_t =10 minutes for (-)-1-[2-[3-(3,4-Dichloro-and phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide.
 The (+)- isomer, (+)-1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide was also
20 obtained, R_t =13 minutes for (+)-1-[2-[3-(3,4-Dichloro-and phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide. (Retention
25 times determined using an analytical CHIRALPAK AD chiral HPLC column (25 cm X 0.46 cm) with 15% methanol in pentane and a flow rate of 1.0 mL/minute.

30

Example 22

Synthesis of 1-[2-[3-phenyl-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide

35

22.1 Synthesis of 3-cyano-3-phenyl-pentanedioic acid diethyl ester

Combined phenylacetonitrile (5.85 g, 50.0 mmol) and THF (30 mL). Cooled in a dry-ice/acetone bath. Added dropwise, sodium bis-(trimethylsilyl)amide (100 mL, 1.0 M in THF, 100 mmol, 2 eq.). After the addition was complete, allowed to warm to ambient temperature. Cooled in a dry-ice/acetone bath. Added dropwise, ethyl bromoacetate (11 mL, 99 mmol). After the addition was complete, warmed to ambient temperature and stir for 3 h. Partitioned the reaction mixture between diethyl ether (200 mL) and water (200 mL). The organic layer was extracted with H₂O (3 X 150 mL), 1N HCl (2 X 100 mL), 5% NaHCO₃ (2 X 100 mL), and brine (1 X 150 mL). Dried over MgSO₄, filtered, and concentrated *in vacuo* to obtain a residue. Chromatographed on silica gel eluting with 20% ethyl acetate in hexane to obtain the title compound:
R_f=0.23 (silica gel, 20% ethyl acetate in hexane).

22.2 Synthesis of [3-phenyl-5-oxo-pyrrolidin-3-yl]-acetic acid ethyl ester

Prepared by the method of example 1.2.2 using 3-cyano-3-phenyl-pentanedioic acid diethyl ester (37 mmol) and Raney nickel (70 g) to give the title compound:
R_f=0.60 (silica gel, 6% methanol in dichloromethane).

22.3 Synthesis of 2-(3-phenyl-5-yl-pyrrolidin-3-yl)-ethanol

Combined (3-phenyl-5-oxo-pyrrolidin-3-yl)-acetic acid ethyl ester (8.71 g, 35 mmol) and LiAlH₄ (141 mL, 1M solution in THF, 141 mmol) in THF (20 mL). Heated to reflux for 19 h. Cooled in an ice bath. Added H₂O (5 mL), NaOH (5 mL, 15%), and H₂O (15 mL). The slurry was filtered and the filtrate was concentrated to obtain a residue. Dissolved the residue in dichloromethane and dried it over MgSO₄, filtered, and concentrated the filtrate *in vacuo* to

obtain a residue which was dried under high vacuum for 24 h to give the title compound:

R_f=0.03 (silica gel, 6% methanol in dichloromethane).

5

22.4 Synthesis of 2-[3-phenyl-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethanol

Prepared by the method of example 3.1 using

10 2-(3-phenyl-pyrrolidin-3-yl)-ethanol (10.47 mmol) and 3,4,5-trimethoxy-benzoyl chloride (10.49 mmol). Chromatographed on silica gel (200 g) eluting with ethyl acetate and then 3% methanol in dichloromethane to give the title compound:

15 R_f=0.38 (silica gel, 6% methanol in dichloromethane).

22.5 Synthesis of 2-[3-phenyl-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate

20

Prepared by the method of example 3.2 using 2-[3-phenyl-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethanol (2.59 mmol) and methanesulfonyl chloride (3.62 mmol) to give the title compound:

25 R_f=0.70 (silica gel, 10% methanol in dichloromethane).

22.6 Synthesis of 1-[2-[3-phenyl-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide

30

Prepared by the method of example 3.3 using

2-[3-phenyl-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate (2.59 mmol) and 4-phenyl-piperidine-4-carboxylic acid amide hydrochloride (3.3 mmol).

35 Chromatography on silica gel (100 g) eluting sequentially with ethyl acetate, 6% methanol in dichloromethane, and 10% methanol in dichloromethane gave the title compound:

R_f=0.41 (silica gel, 10% methanol in dichloromethane).

22A.7 Synthesis of 1-[2-[3-phenyl-1-(3,4,5-
 trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-
5 phenyl-piperidine-4-carboxylic acid amide
 hydrochloride

 Prepared by the method of example 3.3A using
1-[2-[3-phenyl-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-
10 yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide
(710 mg, 1.24 mmol) and dichloromethane saturated with
HCl(gas) (20 mL). The solution was concentrated *in vacuo* to
obtain a residue. The residue was dried under high vacuum
at 56°C for 18 h to afford the title compound:

15 Analysis: calculated for $C_{34}H_{42}ClN_3O_5 \cdot 0.91 H_2O$ C 65.38; H
7.07; N 6.73; Found C 65.00; H 6.97; N 6.49.

Example 23

20

Synthesis of 1-[2-[3-(3,4-dimethoxy-phenyl)-1-(3,4,5-
trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-
piperidine-4-carboxylic acid amide

25 23.1 Synthesis of 3-cyano-3-(3,4-dimethoxy-phenyl)-
 pentanedioic acid diethyl ester

 Combined 3,4-dimethoxy-phenyl-acetonitrile (20.0 g, 113
mmol) and THF (100 mL). Cooled in a dry-ice/acetone bath.
30 Added dropwise, sodium bis(trimethylsilyl)amide (226 mL,
1.0 M in THF, 226 mmol, 2 eq.). After the addition was
complete, allowed to warm to 10 °C. Cooled in a dry-
ice/acetone bath. Added dropwise, ethyl bromoacetate (37.7
g, 226 mmol). After the addition was complete, the
35 reaction mixture was allowed to warm to ambient temperature
and maintained overnight. Filtered the reaction mixture
and concentrated *in vacuo* to obtain a residue. The residue
was partitioned between diethyl ether (600 mL) and water

(200 mL). The organic layer was extracted with water (200 mL), saturated NH_4Cl (2 X 100 mL), dried over MgSO_4 , filtered, and concentrated *in vacuo* to obtain a residue.

- 5 Chromatographed on silica gel eluting with ethyl acetate/hexane (1:2) to obtain the title compound:
 $R_f=0.42$ (silica gel, 1:2 ethyl acetate/hexane).

Analysis: calculated for $\text{C}_{18}\text{H}_{23}\text{NO}_6$ C 61.88; H 6.64; N 4.01; Found C 61.79; H 6.62; N 3.91.

23.2 Synthesis of [3-(3,4-dimethoxy-phenyl)-5-oxo-pyrrolidin-3-yl]-acetic acid ethyl ester

- 15 Combined 3-cyano-3-(3,4-dimethoxy-phenyl)-pentanedioic acid diethyl ester (16.8 g, 48.0 mmol), methanol (300 mL) and cobalt (II) chloride hexahydrate (22.8 g, 96.0 mmol). Cooled until the internal temperature reached 10 °C. Added portionwise so as to maintain the reaction temperature
20 below 20 °C, sodium borohydride (44.2 g, 1.17 mol). After addition was complete, the reaction mixture was allowed to warm to ambient temperature and stirred over the weekend. Concentrated *in vacuo* to obtain a residue. Partitioned
25 between 1N HCl (800 mL) and dichloromethane (800 mL). The organic layer was extracted with 1N HCl (2 X 200 mL). The combined aqueous layers were extracted with dichloromethane (3 X 100 mL). The organic layers were combined, dried over Na_2SO_4 , filtered, and concentrated *in vacuo* to obtain a
30 residue. The residue was chromatographed on silica gel eluting with ethyl acetate/methanol (20:1) to obtain the title compound:
 $R_f=0.27$ (silica gel, 20:1 ethyl acetate/methanol), mp=116-118°C.

- 35 Analysis: calculated for $\text{C}_{16}\text{H}_{21}\text{NO}_5$ C 62.53; H 6.89; N 4.56; Found C 62.52; H 6.85; N 4.50.

23.3 Synthesis of 2-[3-(3,4-dimethoxy-phenyl)-pyrrolidin-3-yl]-ethanol

5 Combined LiAlH₄ (4.80 g, 127 mmol, 4 eq) and anhydrous THF (200 mL). Added portionwise, a slurry of [3-(3,4-dimethoxy-phenyl)-5-oxo-pyrrolidin-3-yl]-acetic acid ethyl ester (9.72 g, 31.6 mmol) in THF (100 mL). After the addition was complete, the reaction was heated at reflux
10 overnight. Cooled in an ice/NaCl bath. Cautiously added H₂O (4.8 mL), NaOH (4.8 mL, 15%), and H₂O (19.2 mL). Filtered. Concentrated the filtrate to obtain a residue. Dissolved the residue in dichloromethane and dried over MgSO₄, filtered, and concentrated the filtrate *in vacuo* to
15 obtain a residue which was dried at 0.05 Torr overnight to give the title compound. This material was used without further purification.

23.4 Synthesis of 2-[3-(3,4-dimethoxy-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethanol

2-[3-(3,4-Dimethoxy-phenyl)-pyrrolidin-3-yl]-ethanol (2.27 g, 9.03 mmol) and dichloromethane (100 mL) were
25 combined. 4-Methylmorpholine (2.28 mL, 22.6 mmol, 2.5 eq.) was added. The mixture was cooled in a ice/NaCl bath and a solution of 3,4,5-trimethoxy-benzoyl chloride (2.19 g, 9.48 mmol) in dichloromethane (30 mL) was added dropwise . After the addition was complete, the dry-ice/acetone bath
30 was changed to an ice bath and the mixture was allowed to warm to ambient temperature and maintained overnight. The solution was extracted with 1N HCl (3 X 100 mL), saturated K₂CO₃ (3 X 100 mL). The organic phase was dried over Na₂SO₄, filtered, and concentrated *in vacuo* to obtain a
35 residue. The residue was purified by chromatography on silica gel eluting with ethyl acetate/methanol (20:1) to obtain a residue. The residue was dissolved in dichloromethane (50 mL), extracted with water (2 X 50 mL),

dried over Na_2SO_4 , filtered, and concentrated *in vacuo* to obtain a residue. Heated at $110^\circ\text{C}/0.3$ Torr for 16 h to obtain the title compound: $R_f=0.14$ (silica gel, 20:1 ethyl acetate/methanol), $\text{mp}=60-62^\circ\text{C}$.

Analysis: calculated for $\text{C}_{24}\text{H}_{31}\text{NO}_7$, C 64.70; H 7.01; N 3.14; Found C 64.40; H 7.21; N 2.85.

10 23.5 Synthesis of 2-[3-(3,4-dimethoxy-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate

Prepared by the method of example 3.2 using
15 2-[3-(3,4-dimethoxy-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethanol (249 mg, 0.55 mmol) and methanesulfonyl chloride (0.76 mmol) to give the title compound:
 $R_f=0.73$ (silica gel, 10% methanol in dichloromethane).

20

23.6 Synthesis of 1-[2-[3-(3,4-dimethoxy-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide

25

Prepared by the method of example 3.3 using
2-[3-(3,4-dimethoxy-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate (0.55 mmol) and 4-phenyl-piperidine-4-carboxylic acid amide hydrochloride
30 (175 mg, 0.73 mmol). Chromatography on silica gel (30 g) eluting sequentially with ethyl acetate, 6% methanol in dichloromethane, and 10% methanol in dichloromethane gave the title compound:
 $R_f=0.39$ (silica gel, 10% methanol in dichloromethane).

35

Analysis: calculated for $\text{C}_{36}\text{H}_{45}\text{N}_3\text{O}_7 \cdot 1.7 \text{ H}_2\text{O}$ C 65.27; H 7.36; N 6.34; Found C 65.26; H 7.02; N 6.32.

Example 24

5 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,5-bis-
 (trifluoromethyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-
 piperidine-4-carboxylic acid amide

10 24.1 Synthesis of 2-[3-(3,4-dichloro-phenyl)-1-(3,5-
 bis-(trifluoromethyl)-benzoyl)-pyrrolidin-3-
 yl]-ethanol

 The method of example 3.1 was used with 2-[3-(3,4-
 dichloro-phenyl)-pyrrolidin-3-yl]-ethanol (1 mmol) and 3,5-
 bis(trifluoromethyl)-benzoyl chloride (1 mmol) to obtain a
15 residue. Chromatography of the residue on silica gel
 eluting sequentially with 1% methanol in dichloromethane
 and then 6% methanol in dichloromethane gave the title
 compound.

 R_f=0.53 (silica gel, 10% methanol in dichloromethane).

20

24.2 Synthesis of 2-[3-(3,4-dichloro-phenyl)-1-(3,5-
 bis-(trifluoromethyl)-benzoyl)-pyrrolidin-3-
 yl]-ethyl-methanesulfonate

25 The method of example 3.2 was used with 2-[3-(3,4-
 dichloro-phenyl)-1-(3,5-bis-(trifluoromethyl)- benzoyl)-
 pyrrolidin-3-yl]-ethanol (0.924 mmol) and methanesulfonyl
 chloride (1.01 mmol) to obtain a residue. Drying the
 residue under high vacuum at ambient temperature 18h gave
30 the title compound.

 R_f=0.68 (silica gel, 10% methanol in dichloromethane).

24.3 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-
 (3,5-bis-(trifluoromethyl)-pyrrolidin-3-yl)-
35 ethyl]-4-phenyl-piperidine-4-carboxylic acid
 amide

The method of example 3.3 was used with 2-[3-(3,4-dichloro-phenyl)-1-(3,5-bis-(trifluoromethyl)-pyrrolidin-3-yl)-ethyl-methanesulfonate (0.87 mmol) 4-phenyl-
5 piperidine-4-carboxylic acid amide hydrochloride (1.04 mmol) to obtain a residue. Chromatography of the residue on silica gel eluting sequentially with 30% ethyl acetate in hexane, 50% ethyl acetate in hexane, 1% methanol in dichloromethane, 3% methanol in dichloromethane, and then
10 6% methanol in dichloromethane gave the title compound: $R_f=0.41$ (silica gel, 10% methanol in dichloromethane).

Example 25

15

Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,5-dimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide

20 25.1 Synthesis of 2-[3-(3,4-dichloro-phenyl)-1-(3,5-dimethoxy-benzoyl)-pyrrolidin-3-yl]-ethanol

The method of example 3.1 was used with 2-[3-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethanol (1 mmol) and 3,5-
25 dimethoxy-benzoyl chloride (1 mmol) to prepare the title compound. Chromatography on silica gel eluting sequentially with ethyl acetate and then 6% methanol in dichloromethane gave the title compound.
 $R_f=0.72$ (silica gel, 10% methanol in dichloromethane).

30

25.2 Synthesis of 2-[3-(3,4-dichloro-phenyl)-1-(3,5-dimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate

35 The method of example 3.2 was used with 2-[3-(3,4-dichloro-phenyl)-1-(3,5-dimethoxy-benzoyl)-pyrrolidin-3-yl]-ethanol (0.96 mmol) and methanesulfonyl chloride (1.06

mmol) to obtain a residue. Drying the residue under high vacuum at ambient temperature 18 h gave the title compound.

5 25.3 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,5-dimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide

10 The method of example 3.3 was used with 2-[3-(3,4-dichloro-phenyl)-1-(3,5-dimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate (0.96 mmol) and 4-phenyl-piperidine-4-carboxylic acid amide hydrochloride (1.06 mmol) to prepare the title compound. Chromatography on
15 silica gel eluting sequentially with ethyl acetate, 6% methanol in dichloromethane, and then 10% methanol in dichloromethane gave the title compound:
R_f=0.55 (silica gel, 10% methanol in dichloromethane).

20

Example 26

Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid (2-dimethylamino-ethyl)-amide

25

26.1 Synthesis of 4-phenyl-piperidine-4-carboxylic acid methyl-ester hydrochloride

4-Phenyl-piperidine-4-carboxylic acid hydrochloride
30 (from example 20.6) (2.67 g, 11 mmol) and methanol (35 mL) were combined. SOCl₂ (0.9 mL, 12.34 mmol, 1.1 eq.) was added dropwise. The reaction was heated at reflux for 18 h. The reaction was concentrated *in vacuo* to obtain a residue. The residue was slurried in diethyl ether,
35 filtered, and the solids were rinsed with diethyl ether to give the title compound.

- 26.2 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid methyl-ester
- 5

The method of example 3.3 was used with 2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate (5 mmol) and 4-phenyl-piperidine-4-carboxylic acid methyl-ester hydrochloride (6 mmol, 1.2 eq.) to obtain a residue. The residue was chromatographed on silica gel eluting sequentially with 1% methanol in dichloromethane and then 2% methanol in dichloromethane to give the title compound:

15 $R_f=0.57$ (silica gel, 6% methanol in dichloromethane).

- 26.3 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid
- 20

1-[2-[3-(3,4-Dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid methyl-ester (0.393 g, 0.60 mmol) and NaOH (6 mL, 1N, 6 mmol) were combined in ethanol (12 mL). The mixture was stirred for 48 h at ambient temperature. 1N HCl was added to adjust the pH to 1. The aqueous phase was extracted with ethyl acetate. The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to obtain a residue. The residue was chromatographed on silica gel eluting sequentially with 10% methanol in dichloromethane and then 20% methanol in dichloromethane. The fractions which contained the title compound were washed with H_2O , dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the title compound:

35 $R_f=0.59$ (silica gel, 85:10:5 $CHCl_3:CH_3OH:CH_3CO_2H$).

- 26FH.4 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-

-145-

ethyl]-4-phenyl-piperidine-4-carboxylic acid
(2-dimethylamino-ethyl)-amide bis-
trifluoroacetate

5

1-[2-[3-(3,4-Dichloro-phenyl)-1-(3,4,5-trimethoxy-
benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-
carboxylic acid (0.2566 g, 0.4 mmol), N,N-dimethylethylene-
diamine (0.05 mL, 0.48 mmol), HOBt (65 mg, 0.48 mmol), EDC
10 (92 mg, 0.48 mmol), DIEA (0.08 mL, 0.48 mmol) were combined
in dichloromethane (20 mL). The mixture was stirred for 72
h at ambient temperature. The mixture was extracted with
H₂O. The organic phase was dried over MgSO₄, filtered, and
concentrated *in vacuo* to obtain a residue. The residue was
15 chromatographed using a Vydac (25 X 250 mm) C-18 HPLC
column to give the title compound:
R_t=28 minutes (gradient elution with CH₃CN/H₂O(0.1% TFA;
flow rate = 1.0 ml/min.) 10% CH₃CN for 10 minutes, 30% CH₃CN
for 15 minutes, 40% CH₃CN for 15 minutes, 50% CH₃CN for 10
20 minutes, and then 100% CH₃CN).

Example 27

Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(3-methoxy-
25 benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-
carboxylic acid amide

27.1 Synthesis of 2-[3-(3,4-dichloro-phenyl)-1-(3-
methoxy-benzoyl)-pyrrolidin-3-yl]-ethanol

30

The method of example 3.1 was used with 2-[3-(3,4-
dichloro-phenyl)-pyrrolidin-3-yl]-ethanol (2 mmol) and 3-
methoxy-benzoyl chloride (2 mmol) to obtain a residue. The
residue was chromatographed on silica gel eluting
35 sequentially with ethyl acetate and then 6% methanol in
dichloromethane to give the title compound.
R_f=0.53 (silica gel, 10% methanol in dichloromethane).

27.2 Synthesis of 2-[3-(3,4-dichloro-phenyl)-1-(3-methoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate

5

The method of example 3.2 was used with 2-[3-(3,4-dichloro-phenyl)-1-(3-methoxy-benzoyl)-pyrrolidin-3-yl]-ethanol (0.6 mmol) and methanesulfonyl chloride (0.66 mmol) to obtain a residue. Drying the residue under high vacuum at ambient temperature for 18 h gave the title compound:

R_f=0.69 (silica gel, 10% methanol in dichloromethane).

27.3 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(3-methoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide

15

The method of example 3.3 was used with 2-[3-(3,4-dichloro-phenyl)-1-(3-methoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate (0.6 mmol) 4-phenyl-piperidine-4-carboxylic acid amide hydrochloride (0.72 mmol) to prepare the title compound. Chromatography on silica gel eluting sequentially with ethyl acetate, 6% methanol in dichloromethane, and then 10% methanol in dichloromethane gave the title compound:

R_f=0.41 (silica gel, 10% methanol in dichloromethane).

30

35

Example 28

5 Synthesis of 1-[2-[3-(benzo[1,3]dioxol-5-yl)-1-(3,4,5-
trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-
piperidine-4-carboxylic acid amide

10 28.1 Synthesis of 3-cyano-3-(benzo[1,3]dioxol-5-yl)-
pentanedioic acid diethyl ester

Combined 3-(benzo[1,3]dioxol-5-yl)-phenylacetonitrile
(25.7 g, 0.159 mol) and THF (200 mL). Cooled in a dry-
ice/acetone bath. Added dropwise, sodium bis-
15 (trimethylsilyl)amide (318 mL, 1.0 M in THF, 0.318 mol, 2
eq.). After the addition was complete, allowed to warm to
10 °C. Cooled in a dry-ice/acetone bath. Added dropwise,
ethyl bromoacetate (35.3 mL, 0.318 mol). After the
addition was complete, warmed to ambient temperature.
20 Removed the THF by evaporation at reduced pressure.
Partitioned the reaction mixture between diethyl ether (200
mL) and water (200 mL). Extracted the organic layer with
saturated NH₄Cl solution (2 x 200 mL). Dried over MgSO₄,
filtered, and concentrated *in vacuo* to obtain a residue.
25 Chromatographed on silica gel eluting with 25% ethyl
acetate in hexane to obtain the title compound:
R_f=0.32 (silica gel, 25% ethyl acetate in hexane).

Analysis: calculated for C₁₇H₁₉NO₆ C 61.25; H 5.75; N
30 4.20; Found C 61.51; H 5.88; N 4.18.

28.2 Synthesis of [3-(benzo[1,3]dioxol-5-yl)-5-oxo-
pyrrolidin-3-yl]-acetic
acid ethyl ester

35

Prepare by the method of example 1.2.2 using 3-cyano-3-
(benzo[1,3]dioxol-5-yl)-pentanedioic acid diethyl ester (89

mmol). Chromatograph on silica gel to give the title compound.

5 28.3 Synthesis of 2-(3-benzo[1,3]dioxol-5-yl-pyrrolidin-3-yl)-ethanol

Prepare by the method of example 1.3.2 using [3-(benzo[1,3]dioxol-5-yl)-5-oxo-pyrrolidin-3-yl]-acetic acid
10 ethyl ester (73 mmol). Chromatograph on silica gel to give the title compound.

28.4 Synthesis of 2-[3-(benzo[1,3]dioxol-5-yl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethanol

15

Prepare by the method of example 3.1 using 2-(3-benzo[1,3]dioxol-5-yl-pyrrolidin-3-yl)-ethanol (23 mmol) and 3,4,5-trimethoxy-benzoyl chloride (23 mmol). Chromatograph on silica gel to give the title compound.

20

28.5 Synthesis of 2-[3-(benzo[1,3]dioxol-5-yl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate

25 Prepare by the method of example 3.2 using 2-[3-(benzo[1,3]dioxol-5-yl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethanol (8 mmol) and methanesulfonyl chloride (11 mmol) to give the title compound.

30 28.6 Synthesis of 1-[2-[3-(benzo[1,3]dioxol-5-yl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide

Prepare by the method of example 3.3 using 2-[3-(benzo[1,3]dioxol-5-yl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate (8 mmol) and 4-phenyl-piperidine-4-carboxylic acid amide hydrochloride (12
35

mmol). Chromatograph on silica gel to give the title compound.

5

Example 29

Synthesis of 1-[2-[3-(3,4-dimethoxy-phenyl)-1-(3,4,5-triethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide

10

29.1 Synthesis of 2-[3-(3,4-dimethoxy-phenyl)-1-(3,4,5-triethoxy-benzoyl)-pyrrolidin-3-yl]-ethanol

2-[3-(3,4-Dimethoxy-phenyl)-pyrrolidin-3-yl]-ethanol
15 (405 mg, 1.61 mmol) and dichloromethane (20 mL) were combined. 4-Methylmorpholine (350 L, 3.22 mmol, 2 eq.) was added. The mixture was cooled in a dry-ice/acetone bath and a solution of 3,4,5-triethoxy-benzoyl chloride (461 mg, 1.69 mmol) in dichloromethane (10 mL) was added dropwise.
20 After the addition was complete, the dry-ice/acetone bath was changed to an ice bath and the mixture was stirred for 1 h. Allowed to warm to ambient temperature and maintained overnight. The solution was extracted with 1N HCl (2 X 50 mL), saturated NaHCO₃ (50 mL), and H₂O (50 mL). The organic
25 phase was dried over Na₂SO₄, filtered, and concentrated *in vacuo* to obtain a residue. The residue was purified by chromatography on silica gel eluting with ethyl acetate/methanol (20:1) to obtain a residue. The residue was dissolved in dichloromethane (50 mL), extracted with
30 water (2 X 50 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo* to obtain a residue. Heated at 70 °C/0.5 Torr for 16 h to obtain the title compound: R_f=0.31 (silica gel, 20:1 ethyl acetate/methanol), mp=139-141°C.

35 29.2 Synthesis of 2-[3-(3,4-dimethoxy-phenyl)-1-(3,4,5-triethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate

Prepare by the method of example 3.2 using 2-[3-(3,4-methoxy-phenyl)-1-(3,4,5-triethoxy-benzoyl)-pyrrolidin-3-yl]-ethanol (8 mmol) and methanesulfonyl chloride (11 mmol) to give the title compound.

29.3 Synthesis of 1-[2-[3-(3,4-dimethoxy-phenyl)-1-(3,4,5-triethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide

10

Prepare by the method of example 3.3 using 2-[3-(3,4-dimethoxy-phenyl)-1-(3,4,5-triethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate (8 mmol) and 4-phenyl-piperidine-4-carboxylic acid amide hydrochloride (12 mmol). Chromatograph on silica gel to give the title compound.

Example 30

20 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-(naphth-2-yl)-piperidine-4-carboxylic acid amide

30.1 Synthesis of 2-chloro-N-(2-chloroethyl)-N-tert-butoxycarbonyl-ethanamine

25

Combine bis-(2-chloroethyl)amine hydrochloride (500 mmol) and dichloromethane (350 mL). Add dropwise, N,N-diisopropylethylamine (1.1 mol). Cool the mixture to -30°C. Add dropwise, a solution of di-tert-butyl dicarbonate (550 mmol) in dichloromethane (100 mL). Stir the mixture and allow it to warm to ambient temperature. Concentrate the mixture *in vacuo* to give a residue. Purify the residue to give the title compound.

35 30.2 Synthesis of 1-tert-butoxycarbonyl-4-cyano-4-(naphth-2-yl)-piperidine

Combine naphth-2-ylacetonitrile (10 mmol) and 2-chloro-N-(2-chloroethyl)-N-*tert*-butoxycarbonyl-ethanamine (11 mmol) in DMSO (30 mL). Add portionwise, NaNH₂ (22 mmol). After the addition, stir for an additional 0.5 h. Pour the contents of the flask over ice (150 g). Extract the mixture with dichloromethane. Dry the organic phase over MgSO₄, filter, and concentrate *in vacuo* to give a residue. Purify to give the title compound.

10

30.3 Synthesis of 4-cyano-4-(naphth-2-yl)-piperidine hydrochloride

Combine 1-*tert*-butoxycarbonyl-4-cyano-4-(naphth-2-yl)-piperidine (3.12 mmol) and HCl in dioxane (10 mL, 40 mmol, 4N, 13 eq.) at ambient temperature for 1 h. Concentrate the solvent *in vacuo* and dry under high vacuum to give the title compound.

20 30.4 Synthesis of 4-(naphth-2-yl)-piperidine-4-carboxylic acid hydrochloride

Prepare by the method of example 20.6 using 4-cyano-4-(naphth-2-yl)-piperidine hydrochloride (10 mmol) and KOH (0.4 mol, 3N). Purify to give the title compound.

25

30.5 Synthesis of 1-*tert*-butoxycarbonyl-4-(naphth-2-yl)-piperidine-4-carboxylic acid

30 Prepare by the method of example 20.7 using 4-(naphth-2-yl)-piperidine-4-carboxylic acid hydrochloride (10 mmol) and di-*tert*-butyl dicarbonate (11 mmol). Purify to give the title compound.

35 30.6 Synthesis of 1-*tert*-butoxycarbonyl-4-(naphth-2-yl)-piperidine-4-carboxylic acid amide

Prepare by the method of example 20.8 using 1-*tert*-butoxycarbonyl-4-(naphth-2-yl)-piperidine-4-carboxylic acid (4 mmol) and NH₃(gas). Purify to give the title compound.

5

30.7 Synthesis of 4-(naphth-2-yl)-piperidine-4-carboxylic acid amide hydrochloride

Prepare by the method of example 20.10 using 1-*tert*-butoxycarbonyl-4-(naphth-2-yl)-piperidine-4-carboxylic acid amide (3 mmol) and HCl in dioxane (40 mmol, 4N) to give the title compound.

15

30.8 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-(naphth-2-yl)-piperidine-4-carboxylic acid amide

Prepare by the method of example 3.3 using 2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate (5 mmol) and 4-(naphth-2-yl)-piperidine-4-carboxylic acid amide hydrochloride (7.5 mmol, 1.5 eq.). Chromatograph on silica gel to give the title compound.

25

Example 31

Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-(pyridin-4-yl)-piperidine-4-carboxylic acid amide

30

31.1 Synthesis of 1-*tert*-butoxycarbonyl-4-cyano-4-(pyridin-4-yl)-piperidine

Prepare by the method of example 30.2 using 4-pyridylacetonitrile (10 mmol) and 2-chloro-N-(2-chloroethyl)-N-*tert*-butoxycarbonyl-ethanamine (11 mmol). Purify to give the title compound.

35

31.2 Synthesis of 4-cyano-4-(pyridin-4-yl)-piperidine hydrochloride

5 Prepare by the method of example 30.3 using 1-*tert*-butoxycarbonyl-4-cyano-4-(pyridin-4-yl)-piperidine (3 mmol) and HCl in dioxane (40 mmol, 4N). Concentrate the solvent *in vacuo* and dry under high vacuum to give the title compound.

10

31.3 Synthesis of 4-(pyridin-4-yl)-piperidine-4-carboxylic acid hydrochloride

15 Prepare by the method of example 20.6 using 4-cyano-4-(pyridin-4-yl)-piperidine hydrochloride (10 mmol) and KOH (0.4 mol, 3N). Purify to give the title compound.

31.4 Synthesis of 1-*tert*-butoxycarbonyl-4-(pyridin-4-yl)-piperidine-4-carboxylic acid

20

Prepare by the method of example 20.7 using 4-(pyridin-4-yl)-piperidine-4-carboxylic acid hydrochloride (10 mmol) and di-*tert*-butyl dicarbonate (11 mmol). Purify to give the title compound.

25

31.5 Synthesis of 1-*tert*-butoxycarbonyl-4-(pyridin-4-yl)-piperidine-4-carboxylic acid amide

30 Prepare by the method of example 20.8 using 1-*tert*-butoxycarbonyl-4-(pyridin-4-yl)-piperidine-4-carboxylic acid (4.0 mmol) and NH₃(gas). Purify to give the title compound.

31.6 Synthesis of 4-(pyridin-4-yl)-piperidine-4-carboxylic acid amide hydrochloride

35

Prepare by the method of example 20.10 using 1-*tert*-butoxycarbonyl-4-(pyridin-4-yl)-piperidine-4-carboxylic

acid amide (3 mmol) and HCl in dioxane (40 mmol, 4N) to give the title compound.

5 31.7 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-(pyridin-4-yl)-piperidine-4-carboxylic acid amide

10 Prepare by the method of example 3.3 using 2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate (5 mmol) and 4-(pyridin-4-yl)-piperidine-4-carboxylic acid amide hydrochloride (7.5 mmol, 1.5 eq.). Chromatograph on silica gel to give the title compound.

15

Example 32

20 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-(pyridin-3-yl)-piperidine-4-carboxylic acid amide

32.1 Synthesis of 1-tert-Butoxycarbonyl-4-cyano-4-(pyridin-3-yl)-piperidine

25 Prepare by the method of example 30.2 using 3-pyridylacetonitrile (10 mmol) and 2-chloro-N-(2-chloroethyl)-N-tert-butoxycarbonyl-ethanamine (11 mmol). Purify to give the title compound.

30 32.2 Synthesis of 4-cyano-4-(pyridin-3-yl)-piperidine hydrochloride

35 Prepare by the method of example 30.3 using 1-tert-butoxycarbonyl-4-cyano-4-(pyridin-3-yl)-piperidine (3 mmol) and HCl in dioxane (40 mmol, 4N). Concentrate the solvent *in vacuo* and dry under high vacuum to give the title compound.

32.3 Synthesis of 4-(pyridin-3-yl)-piperidine-4-carboxylic acid hydrochloride

5 Prepare by the method of example 20.6 using 4-cyano-4-(pyridin-3-yl)-piperidine hydrochloride (10 mmol) and KOH (0.4 mol, 3N). Purify to give the title compound.

32.4 Synthesis of 1-tert-butoxycarbonyl-4-(pyridin-3-yl)-piperidine-4-carboxylic acid

10 Prepare by the method of example 20.7 using 4-(pyridin-3-yl)-piperidine-4-carboxylic acid hydrochloride (10 mmol) and di-tert-butyl dicarbonate (11 mmol). Purify to give the title compound.

32.5 Synthesis of 1-tert-butoxycarbonyl-4-(pyridin-3-yl)-piperidine-4-carboxylic acid amide

20 Prepare by the method of example 20.8 using 1-tert-butoxycarbonyl-4-(pyridin-3-yl)-piperidine-4-carboxylic acid (4.0 mmol) and NH₃(gas). Purify to give the title compound.

25 32.6 Synthesis of 4-(pyridin-3-yl)-piperidine-4-carboxylic acid amide hydrochloride

30 Prepare by the method of example 20.10 using 1-tert-butoxycarbonyl-4-(pyridin-3-yl)-piperidine-4-carboxylic acid amide (3 mmol) and HCl in dioxane (40 mmol, 4N) to give the title compound.

32.7 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-(pyridin-3-yl)-piperidine-4-carboxylic acid amide

35 Prepare by the method of example 3.3 using 2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-

yl]-ethyl-methanesulfonate (5 mmol) and 4-(pyridin-3-yl)-
piperidine-4-carboxylic acid amide hydrochloride (7.5 mmol,
1.5 eq.). Chromatograph on silica gel to give the title
5 compound.

Example 33

Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-
10 trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-(pyridin-2-
yl)-piperidine-4-carboxylic acid amide

33.1 Synthesis of 1-tert-butoxycarbonyl-4-cyano-4-
15 (pyridin-2-yl)-piperidine

Prepare by the method of example 30.2 using 2-
pyridylacetonitrile (10 mmol) and 2-chloro-N-(2-
chloroethyl)-N-tert-Butoxycarbonyl-ethanamine (11 mmol).
Purify to give the title compound.

20 33.2 Synthesis of 4-cyano-4-(pyridin-2-yl)-piperidine
hydrochloride

Prepare by the method of example 30.3 using 1-tert-
25 butoxycarbonyl-4-cyano-4-(pyridin-2-yl)-piperidine (3 mmol)
and HCl in dioxane (40 mmol, 4N). Concentrate the solvent
in vacuo and dry under high vacuum to give the title
compound.

30 33.3 Synthesis of 4-(pyridin-2-yl)-piperidine-4-
carboxylic acid hydrochloride

Prepare by the method of example 20.6 using 4-cyano-4-
(pyridin-2-yl)-piperidine hydrochloride (10 mmol) and KOH
35 (0.4 mol, 3N). Purify to give the title compound.

33.4 Synthesis of 1-tert-butoxycarbonyl-4-(pyridin-2-yl)-
piperidine-4-carboxylic acid

Prepare by the method of example 20.7 using 4-(pyridin-2-yl)-piperidine-4-carboxylic acid hydrochloride (10 mmol) and di-*tert*-butyl dicarbonate (11 mmol). Purify to give the title compound.

33.5 Synthesis of 1-*tert*-butoxycarbonyl-4-(pyridin-2-yl)-piperidine-4-carboxylic acid amide

10

Prepare by the method of example 20.8 using 1-*tert*-butoxycarbonyl-4-(pyridin-2-yl)-piperidine-4-carboxylic acid (4 mmol) and NH₃(gas). Purify to give the title compound.

15

33.6 Synthesis of 4-(pyridin-2-yl)-piperidine-4-carboxylic acid amide hydrochloride

Prepare by the method of example 20.10 using 1-*tert*-butoxycarbonyl-4-(pyridin-2-yl)-piperidine-4-carboxylic acid amide (3 mmol) and HCl in dioxane (40 mmol, 4N) to give the title compound.

33.7 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-(pyridin-2-yl)-piperidine-4-carboxylic acid amide

Prepare by the method of example 3.3 using 2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate (5 mmol) and 4-(pyridin-2-yl)-piperidine-4-carboxylic acid amide hydrochloride (7.5 mmol, 1.5 eq.). Chromatograph on silica gel to give the title compound.

35

Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-benzyl-piperidine-4-carboxylic acid amide

5

34.1 Synthesis of ethyl-(1-tert-butoxycarbonyl-piperidine)-4-carboxylate

Combine ethyl-piperidine-4-carboxylate (10 mmol) and
10 dichloromethane (50 mL). Add dropwise, N,N-diisopropylethylamine (11 mmol). Add dropwise, a solution of di-tert-butyl dicarbonate (11 mmol) in dichloromethane (10 mL). Stir the mixture at ambient temperature. Extract the
15 mixture with 1N HCl and H₂O. Dry the organic phase over MgSO₄, filter, and concentrate *in vacuo* to give a residue. Purify the residue to give the title compound.

34.2 Synthesis of ethyl-(4-benzyl-1-tert-butoxycarbonyl-piperidine)-4-carboxylate

20 Combine lithium diisopropylamide (11 mmol) and THF (100 mL). Cool in a dry-ice/acetone bath. Add ethyl-(1-tert-butoxycarbonyl-piperidine)-4-carboxylate (10 mmol). Stir for 2 h. Add dropwise, benzyl bromide (12 mmol) in hexamethylphosphoramide (3 mmol). Stir and allow the
25 mixture to warm slowly. Dilute with ethyl acetate and extract with H₂O. Dry the organic phase over MgSO₄, filter, and concentrate *in vacuo* to give a residue. Purify the residue to give the title compound.

30 34.3 Synthesis of 4-benzyl-1-tert-butoxycarbonyl-piperidine)-4-carboxylic acid

Combine ethyl-(4-benzyl-1-tert-butoxycarbonyl-piperidine)-4-carboxylate (0.60 mmol) and NaOH (6 mL, 1N, 6
35 mmol) in ethanol (12 mL). Stir the mixture at ambient temperature. Add 1N HCl to adjust the pH to 1. Extract the aqueous phase with ethyl acetate. Dry the organic

phase over MgSO₄, filter, and concentrate *in vacuo* to obtain a residue. Purify the residue to give the title compound.

5 34.4 Synthesis of 4-benzyl-1-*tert*-butoxycarbonyl-piperidine)-4-carboxylic acid amide

Prepare by the method of example 20.8 using 4-benzyl-1-*tert*-butoxycarbonyl-piperidine-4-carboxylic acid
10 (4.0 mmol) and NH₃(gas). Purify to give the title compound.

34.5 Synthesis of 4-benzyl-piperidine-4-carboxylic acid amide

15

Prepare by the method of example 20.10 using 4-benzyl-1-*tert*-butoxycarbonyl-piperidine)-4-carboxylic acid amide (3 mmol) and HCl in dioxane (40 mmol, 4N) to give the title compound.

20

34.6 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-benzyl-piperidine-4-carboxylic acid amide

25

Prepare by the method of example 3.3 using 2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate (5 mmol) and 4-benzyl-piperidine-4-carboxylic acid amide hydrochloride (7.5 mmol,
30 1.5 eq.). Chromatograph on silica gel to give the title compound.

Example 35

35 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid pyrrolidine-amide

- 35.1 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid pyrrolidine-
5 amide

Prepare by the method of example 3.3 using 2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate (5 mmol) and 4-phenyl-
10 piperidine-4-carboxylic acid pyrrolidine-amide hydrochloride (7.5 mmol, 1.5 eq.). Chromatograph on silica gel to give the title compound.

Example 36

15

Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid morpholine-amide

- 20 36.1 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid
 morpholine-amide

25 Prepare by the method of example 3.3 using 2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate (5 mmol) and 4-phenyl-piperidine-4-carboxylic acid morpholine-amide hydrochloride (7.5 mmol, 1.5 eq.). Chromatograph on silica gel to give
30 the title compound.

Example 37

Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid piperidine-amide

35

- 37.1 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid piperidine-
5 amide

Prepare by the method of example 3.3 using 2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate (5 mmol) and 4-phenyl-
10 piperidine-4-carboxylic acid piperidine-amide hydrochloride (7.5 mmol, 1.5 eq.). Chromatograph on silica gel to give the title compound.

Example 38

- 15 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid methyl-amide

- 20 38.1 Synthesis of 1-tert-butoxycarbonyl-4-phenyl-piperidine-4-carboxylic acid methyl-amide

Prepare by the method of example 20.8 using 1-tert-butoxycarbonyl-4-phenyl-piperidine-4-carboxylic acid (4.0
25 mmol) and CH₃NH₂. Purify to give the title compound.

- 38.2 Synthesis of 4-phenyl-piperidine-4-carboxylic acid methyl-amide

30 Prepare by the method of example 20.10 using 4-phenyl-1-tert-butoxycarbonyl-piperidine-4-carboxylic acid methyl-amide (3 mmol) and HCl in dioxane (40 mmol, 4N) to give the title compound.

- 35 38.3 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid methyl-amide

Prepare by the method of example 3.3 using 2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate (5 mmol) and 4-phenyl-piperidine-4-carboxylic acid methyl-amide hydrochloride (7.5 mmol, 1.5 eq.). Chromatograph on silica gel to give the title compound.

Example 39

10

Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid dimethyl-amide

15 39.1 Synthesis of 1-tert-butoxycarbonyl-4-phenyl-piperidine-4-carboxylic acid dimethyl-amide

Prepare by the method of example 20.8 using 1-tert-butoxycarbonyl-4-phenyl-piperidine-4-carboxylic acid (4.0 mmol) and $(\text{CH}_3)_2\text{NH}$. Purify to give the title compound.

39.2 Synthesis of 4-phenyl-piperidine-4-carboxylic acid dimethyl-amide

25 Prepare by the method of example 20.10 using 4-phenyl-1-tert-butoxycarbonyl-piperidine)-4-carboxylic acid dimethyl-amide (3 mmol) and HCl in dioxane (40 mmol, 4N) to give the title compound.

30 39.3 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid dimethyl-amide

35 Prepare by the method of example 3.3 using 2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate (5 mmol) and 4-phenyl-piperidine-4-carboxylic acid dimethyl-amide hydrochloride

(7.5 mmol, 1.5 eq.). Chromatograph on silica gel to give the title compound.

5

Example 40

Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(4-chloro-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide

10

40.1 Synthesis of 2-[3-(3,4-dichloro-phenyl)-1-(4-chloro-benzoyl)-pyrrolidin-3-yl]-ethanol

15 Prepare by the method of example 3.1 using 2-[3-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethanol (2 mmol) and 4-chlorobenzoyl chloride (2 mmol). Chromatograph on silica gel to give the title compound.

20 40.2 Synthesis of 2-[3-(3,4-dichloro-phenyl)-1-(4-chloro-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate

25 Prepare by the method of example 3.2 using 2-[3-(3,4-dichloro-phenyl)-1-(4-chloro-benzoyl)-pyrrolidin-3-yl]-ethanol (0.6 mmol) and methanesulfonyl chloride (0.66 mmol). Dry the residue under high vacuum at ambient temperature 18 h to obtain the title compound.

30 40.3 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(4-chloro-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide

35 Prepare by the method of example 3.3 using 2-[3-(3,4-dichloro-phenyl)-1-(4-chloro-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate (0.6 mmol) and 4-phenyl-piperidine-4-carboxylic acid amide hydrochloride (0.72 mmol). Chromatograph on silica gel to give the title compound.

Example 41

5 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(4-tert-butyl-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide

10 41.1 Synthesis of 2-[3-(3,4-dichloro-phenyl)-1-(4-tert-butyl-benzoyl)-pyrrolidin-3-yl]-ethanol

Prepare by the method of example 3.1 using 2-[3-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethanol (2 mmol) and 4-tert-butyl-benzoyl chloride (2 mmol). Chromatograph on silica gel to give the title compound.

15 41.2 Synthesis of 2-[3-(3,4-dichloro-phenyl)-1-(4-tert-butyl-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate

20 Prepare by the method of example 3.2 using 2-[3-(3,4-dichloro-phenyl)-1-(4-tert-butyl-benzoyl)-pyrrolidin-3-yl]-ethanol (0.6 mmol) and methanesulfonyl chloride (0.66 mmol). Dry the residue under high vacuum at ambient temperature 18 h to obtain the title compound.

25 41.3 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(4-tert-butyl-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide

30 Prepare by the method of example 3.3 using 2-[3-(3,4-dichloro-phenyl)-1-(4-tert-butyl-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate (0.6 mmol) and 4-phenyl-piperidine-4-carboxylic acid amide hydrochloride (0.72 mmol). Chromatograph on silica gel to give the title compound.

Example 42

5 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(4-*tert*-butyl-phenacyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide

10 42.1 Synthesis of 2-[3-(3,4-dichloro-phenyl)-1-(4-*tert*-butyl-phenacyl)-pyrrolidin-3-yl]-ethanol

Prepare by the method of example 3.1 using 2-[3-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethanol (2 mmol) and 4-*tert*-butyl-phenacyl chloride (2 mmol). Chromatograph on
15 silica gel to give the title compound.

20 42.2 Synthesis of 2-[3-(3,4-dichloro-phenyl)-1-(4-*tert*-butyl-phenacyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate

Prepare by the method of example 3.2 using 2-[3-(3,4-dichloro-phenyl)-1-(4-*tert*-butyl-phenacyl)-pyrrolidin-3-yl]-ethanol (0.6 mmol) and methanesulfonyl chloride (0.66 mmol). Dry the residue under high vacuum at ambient
25 temperature for 18 h to obtain the title compound.

42.3 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(4-*tert*-butyl-phenacyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide

30 Prepare by the method of example 3.3 using 2-[3-(3,4-dichloro-phenyl)-1-(4-*tert*-butyl-phenacyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate (0.6 mmol) and 4-phenyl-piperidine-4-carboxylic acid amide hydrochloride (0.72 mmol). Chromatograph on silica gel to give the title compound.

35

Example 43

5 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(3-isopropoxy-phenacyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide

10 43.1 Synthesis of 2-[3-(3,4-dichloro-phenyl)-1-(3-isopropoxy-phenacyl)-pyrrolidin-3-yl]-ethanol

Prepare by the method of example 3.1 using 2-[3-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethanol (2 mmol) and 3-isopropoxy-phenacyl chloride (2 mmol). Chromatograph on
15 silica gel to give the title compound.

20 43.2 Synthesis 2-[3-(3,4-dichloro-phenyl)-1-(3-isopropoxy-phenacyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate

Prepare by the method of example 3.2 using 2-[3-(3,4-dichloro-phenyl)-1-(3-isopropoxy-phenacyl)-pyrrolidin-3-yl]-ethanol (0.6 mmol) and methanesulfonyl chloride (0.66 mmol). Dry the residue under high vacuum at ambient
25 temperature 18 h to obtain the title compound.

30 43.3 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(3-isopropoxy-phenacyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide

Prepare by the method of example 3.3 using 2-[3-(3,4-dichloro-phenyl)-1-(3-isopropoxy-phenacyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate (0.6 mmol) and 4-phenyl-piperidine-4-carboxylic acid amide hydrochloride (0.72 mmol). Chromatograph on silica gel to give the title
35 compound.

Example 44

5 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-
 trimethoxy-phenacyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-
 piperidine-4-carboxylic acid amide

10 44.1 Synthesis of 2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-
 trimethoxy-phenacyl)-pyrrolidin-3-yl]-ethanol

 Prepare by the method of example 3.1 using 2-[3-(3,4-
dichloro-phenyl)-pyrrolidin-3-yl]-ethanol (2 mmol) and
3,4,5-trimethoxy-phenacyl chloride (2 mmol). Chromatograph
15 on silica gel to give the title compound.

44.2 2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-
 phenacyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate

20 Prepare by the method of example 3.2 using 2-[3-(3,4-
dichloro-phenyl)-1-(3,4,5-trimethoxy-phenacyl)-pyrrolidin-
3-yl]-ethanol (0.6 mmol) and methanesulfonyl chloride
(0.66 mmol). Dry the residue under high vacuum at ambient
temperature 18 h to obtain the title compound.

25

44.3 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-
 (3,4,5-trimethoxy-phenacyl)-pyrrolidin-3-yl]-
 ethyl]-4-phenyl-piperidine-4-carboxylic
 acid amide

30

 Prepare by the method of example 3.3 using 2-[3-(3,4-
dichloro-phenyl)-1-(3,4,5-trimethoxy-phenacyl)-pyrrolidin-
3-yl]-ethyl-methanesulfonate (0.6 mmol) and 4-phenyl-
piperidine-4-carboxylic acid amide hydrochloride (0.72
35 mmol). Chromatograph on silica gel to give the title
compound.

Example 45

5 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(pyridine-2-carbonyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide

10 45.1 Synthesis of 2-[3-(3,4-dichloro-phenyl)-1-(pyridine-2-carbonyl)-pyrrolidin-3-yl]-ethanol

Prepare by the method of example 3.1 using 2-[3-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethanol (2 mmol) and 2-pyridinecarbonyl chloride (2 mmol). Chromatograph on
15 silica gel to give the title compound.

20 45.2 Synthesis of 2-[3-(3,4-dichloro-phenyl)-1-(pyridine-2-carbonyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate

Prepare by the method of example 3.2 using 2-[3-(3,4-dichloro-phenyl)-1-(pyridine-2-carbonyl)-pyrrolidin-3-yl]-ethanol (0.6 mmol) and methanesulfonyl chloride (0.66 mmol). Dry the residue under high vacuum at ambient
25 temperature 18 h to obtain the title compound.

30 45.3 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(pyridine-2-carbonyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide

Prepare by the method of example 3.3 using 2-[3-(3,4-dichloro-phenyl)-1-(pyridine-2-carbonyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate (0.6 mmol) and 4-phenyl-piperidine-4-carboxylic acid amide hydrochloride (0.72 mmol).
35 Chromatograph on silica gel to give the title compound.

Example 46

5 Synthesis of 8-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one

10 46.1 Synthesis of 8-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one

Prepare by the method of example 3.3 using 2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate (5 mmol) and 1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one hydrochloride (7.5 mmol, 1.5 eq.). Chromatograph on silica gel to give the title compound.

20

Example 47

Synthesis of 8-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]dec-2-en-4-one

25

47.1 Synthesis of 1-benzyl-4-(4-fluoro-phenylamino)-piperidine-4-carbonitrile

Combine 1-benzyl-4-oxo-piperidine (100 mmol), 4-fluorophenylamine (110 mmol), and toluene (300 mL). Heat at reflux for 3 h with azeotropic removal of water. Cool to 50°C. Add acetone cyanohydrin (277 mmol). Slowly distill away the acetone. Concentrate the solvent *in vacuo* to obtain a residue. Chromatograph on silica gel to obtain the title compound.

47.2 Synthesis of 1-benzyl-4-(4-fluoro-phenylamino)-piperidine-4-carboxylic acid amide

Cautiously combine 1-benzyl-4-(4-fluoro-phenylamino)-piperidine-4-carbonitrile (60 mmol) and concentrated
5 sulfuric acid (270 mL). Let stand for 24 h at ambient temperature. Cautiously pour the reaction mixture into excess dilute ammonium hydroxide solution/ice. Extract with dichloromethane (3 X 300 mL). Combine the dichloromethane extracts and extract them using saturated
10 NaHCO₃ solution (3 X 300 mL). Dry the dichloromethane solution over magnesium sulfate, filter, and concentrate *in vacuo* to obtain a residue. Purify to obtain the title compound.

15 47.3 Synthesis of 8-benzyl-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]dec-2-en-4-one

Mix 1-benzyl-4-(4-fluoro-phenylamino)-piperidine-4-carboxylic acid amide (20 mmol) and hot toluene (240 mL).
20 Add dimethoxy-N,N-dimethylmethanamine (20 mL) and heat at reflux for 48 h. Concentrate *in vacuo* to obtain a residue. Purify to obtain the title compound.

25 47.4 Synthesis of 1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]dec-2-en-4-one hydrochloride

Combine 8-benzyl-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]dec-2-en-4-one (10 mmol) and 1,2-dichloroethane (70 mL). Cool using an ice bath. Add in dropwise fashion,
30 1-chloroethyl chloroformate (48.6 mmol). Warm to ambient temperature and maintain for 1 h. Extract using saturated NaHCO₃ (120 mL). Extract the aqueous phase using dichloromethane (120 mL). Combine the organic layers, extract with saturated NaCl, dry over Na₂SO₄, filter, and
35 concentrate *in vacuo* to obtain a residue. Add anhydrous methanol (70 mL) and heat at reflux for 1 h. Concentrate *in vacuo* to obtain a residue and purify to obtain the title compound.

47.5 Synthesis of 8-[2-[3-(3,4-dichloro-phenyl)-1-
(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-
5 1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]dec-2-
en-4-one

Prepare by the method of example 3.3 using
2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-
10 pyrrolidin-3-yl]-ethyl-methanesulfonate (5 mmol) and 1-(4-
fluoro-phenyl)-1,3,8-triaza-spiro[4.5]dec-2-en-4-one
hydrochloride (7.5 mmol, 1.5 eq.). Chromatograph on silica
gel to give the title compound.

15 Example 48

Synthesis of 8-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one

48.1 1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-
one

Mix 8-benzyl-1-(4-fluoro-phenyl)-1,3,8-triaza-
25 spiro[4.5]dec-2-en-4-one (20 mmol) and methanol (200 mL).
Add to a catalytic amount of PtO₂ and hydrogenate at 50
psi. Remove the PtO₂ by filtration and concentrate *in vacuo*
to obtain a residue. Purify to obtain the title compound.

30 48.2 Synthesis of 8-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one

35 Prepare by the method of example 3.3 using
2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-
pyrrolidin-3-yl]-ethyl-methanesulfonate (5 mmol) and 1-(4-
fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one (7.5

mmol, 1.5 eq.). Chromatograph on silica gel to give the title compound.

5

Example 49

Synthesis of 3-benzyl-8-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one

10

49.1 Synthesis of 8-*tert*-butoxycarbonyl-1-(4-fluoro-phenyl)-4-oxo-1,3,8-triaza-spiro[4.5]decane

Combine 1-2-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one (15 mmol), di-*tert*-butyl dicarbonate (16 mmol), and chloroform (100 mL). After 24 h, concentrate *in vacuo* to obtain a residue. Purify to obtain the title compound.

20 49.2 Synthesis of 8-*tert*-butoxycarbonyl-3-benzyl-1-(4-fluoro-phenyl)-4-oxo-1,3,8-triaza-spiro[4.5]decane

Combine 8-*tert*-butoxycarbonyl-1-(4-fluoro-phenyl)-4-oxo-1,3,8-triaza-spiro[4.5]decane (12 mmol) and DMF (20 mL).
25 Cool in an ice bath. Add NaH (18 mmol) in several portions. After the addition is complete, add benzyl bromide (18 mmol). Allow the reaction mixture to warm to ambient temperature. After 3 h, cool the reaction vessel using an ice bath and cautiously add 10% aqueous citric
30 acid (20 mL). When gas evolution has ceased, pour into an additional 20 mL of 10% aqueous citric acid and extract using ethyl acetate (3 X 60 mL). Extract the combined organics with saturated aqueous NaCl, dry over Na₂SO₄, filter, and concentrate *in vacuo* to obtain a residue. Purify
35 to obtain the title compound.

49.3 Synthesis of 3-benzyl-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one

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Cool trifluoroacetic acid (20 mL) using an ice bath and add 8-*tert*-butoxycarbonyl-3-benzyl-1-(4-fluoro-phenyl)-4-oxo-1,3,8-triaza-spiro[4.5]decane (10 mmol). After 1 h, dilute with diethyl ether (150 mL), filter to obtain a residue. Purify to obtain the title compound.

49.4 Synthesis of 3-benzyl-8-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one

Prepare by the method of example 3.3 using 2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate (5 mmol) and 3-benzyl-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one trifluoroacetate (7.5 mmol, 1.5 eq.). Chromatograph on silica gel to give the title compound.

Example 50

Synthesis of 3-benzyl-8-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decane-2,4-dione

50.1 Synthesis of 8-benzyl-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decane-2,4-dione

Combine 1-benzyl-4-(4-fluoro-phenylamino)-piperidine-4-carbonitrile (32 mmol) and dichloromethane (100 mL). Add chlorosulfonyl isocyanate (20 mmol) in dropwise fashion with water bath cooling so as to maintain the temperature of the reaction mixture between 20 and 30 °C. After 30 minutes, concentrate the reaction mixture *in vacuo* to obtain a residue. Add 1N HCl (100 mL) and heat at reflux for 1 h. Cool in an ice bath and adjust the pH to 5.5 using 5N NaOH.

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Filter to obtain a residue. Wash with diethyl ether and dry *in vacuo*. Purify to obtain the title compound.

5 50.2 Synthesis of 3,8-dibenzyl-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decane-2,4-dione

Combine 8-benzyl-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decane-2,4-dione (12 mmol) and DMF (20 mL). Cool
10 in an ice bath. Add NaH (18 mmol) in several portions. After the addition is complete, add benzyl bromide (18 mmol). Allow the reaction mixture to warm to ambient temperature. After 3 h, cool the reaction vessel using an ice bath and cautiously add 10% aqueous citric acid (20
15 mL). When gas evolution has ceased, pour into an additional 20 mL of 10% aqueous citric acid and extract using ethyl acetate (3 X 60 mL). Extract the combined organics with saturated aqueous NaCl, dry over Na₂SO₄, filter, and concentrate *in vacuo* to obtain a residue. Purify
20 to obtain the title compound.

50.3 Synthesis of 3-benzyl-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decane-2,4-dione

25 Combine 3,8-dibenzyl-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decane-2,4-dione (10 mmol) and 1,2-dichloroethane (70 mL). Cool using an ice bath. Add in dropwise fashion, 1-chloroethyl chloroformate (48.6 mmol). Warm to ambient temperature and maintain for 1 h. Extract using saturated
30 NaHCO₃ (120 mL). Extract the aqueous phase using dichloromethane (120 mL). Combine the organic layers, extract with saturated NaCl, dry over Na₂SO₄, filter, and concentrate *in vacuo* to obtain a residue. Add anhydrous methanol (70 mL) and heat at reflux for 1 h. Concentrate *in*
35 *vacuo* to obtain a residue and purify to obtain the title compound.

- 50.4 Synthesis of 3-benzyl-8-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decane-2,4-dione
- 5

Prepare by the method of example 3.3 using 2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate (5 mmol) and 3-benzyl-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decane-2,4-dione hydrochloride (7.5 mmol, 1.5 eq.). Chromatograph on silica gel to give the title compound.

Example 51

15

Synthesis of 8-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decane-2,4-dione

- 20 51.1 Synthesis of 1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decane-2,4-dione

Combine 8-benzyl-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decane-2,4-dione (10 mmol) and 1,2-dichloroethane (70 mL). Cool using an ice bath. Add in dropwise fashion, 1-chloroethyl chloroformate (48.6 mmol). Warm to ambient temperature and maintain for 1 h. Extract using saturated NaHCO₃ (120 mL). Extract the aqueous phase using dichloromethane (120 mL). Combine the organic layers, extract with saturated NaCl, dry over Na₂SO₄, filter, and concentrate *in vacuo* to obtain a residue. Add anhydrous methanol (70 mL) and heat at reflux for 1 h. Concentrate *in vacuo* to obtain a residue and purify to obtain the title compound.

35

- 51.2 Synthesis of 8-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-

1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decane-2,4-dione

- 5 Combine the 2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate (5.0 mmol), 1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decane-2,4-dione hydrochloride (7.5 mmol, 1.5 eq.), N,N-diisopropylethylamine (15 mmol), and DMF (8 mL).
- 10 Heat the mixture at 85°C for 48 h. Cool to ambient temperature and add ethyl acetate (100 mL). Extract with water (25 mL), 1N HCl (2 X 25 mL), saturated NaHCO₃ (25 mL), and saturated NaCl (25 mL). Dry over MgSO₄, filter, and concentrate *in vacuo* to obtain a residue. Purify to obtain
- 15 the title compound.

Example 52

20 Synthesis of 1-[2-[3-(3-trifluoromethyl-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide

25 52.1 Synthesis of 3-cyano-3-(3-trifluoromethyl-phenyl)-pentanedioic acid diethyl ester

Prepare by the method of example 1.1.2 using 3-trifluoromethyl-phenylacetonitrile (0.161 mol) and ethyl bromoacetate (0.325 mol). Chromatograph on silica gel to give the title compound.

30

52.2 Synthesis of [3-(3-trifluoromethyl-phenyl)-5-oxo-pyrrolidin-3-yl]-acetic acid ethyl ester

Prepare by the method of example 1.2.2 using

35 3-cyano-3-(3-trifluoromethyl-phenyl)-pentanedioic acid diethyl ester (89 mmol). Chromatograph on silica gel to give the title compound.

52.3 Synthesis of 2-[3-(3-trifluoromethyl-phenyl)-pyrrolidin-3-yl]-ethanol

5 Prepare by the method of example 1.3.2 using [3-(3-trifluoromethyl-phenyl)-5-oxo-pyrrolidin-3-yl]-acetic acid ethyl ester (73 mmol). Chromatograph on silica gel to give the title compound.

10 52.4 Synthesis of 2-[3-(3-trifluoromethyl-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethanol

 Prepare by the method of example 3.1 using 2-[3-(3-trifluoromethyl-phenyl)-pyrrolidin-3-yl]-ethanol (23 mmol) and 3,4,5-trimethoxy-benzoyl chloride (23 mmol). Chromatograph on silica gel to give the title compound.

20 52.5 Synthesis of 2-[3-(3-trifluoromethyl-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate

 Prepare by the method of example 3.2 using 2-[3-(3-trifluoromethyl-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethanol (8 mmol) and methanesulfonyl chloride (11 mmol) to give the title compound.

30 52.6 Synthesis of 1-[2-[3-(3-trifluoromethyl-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide

 Prepare by the method of example 3.3 using 2-[3-(3-trifluoromethyl-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate (8 mmol) and 4-phenyl-piperidine-4-carboxylic acid amide hydrochloride (12 mmol). Chromatograph on silica gel to give the title compound.

Example 53

5 Synthesis of 1-[2-[3-(thiophen-2-yl)-1-(3,4,5-trimethoxy-
benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-
carboxylic acid amide

10 53.1 Synthesis of 3-cyano-3-(thiophen-2-yl)-pentanedioic
acid diethyl ester

Prepare by the method of example 1.1.2 using thiophen-2-yl-acetonitrile (0.161 mol) and ethyl bromoacetate (0.325 mol). Chromatograph on silica gel to give the title compound.

15 53.2 Synthesis of [3-(thiophen-2-yl)-5-oxo-pyrrolidin-3-
yl]-acetic acid ethyl ester

Prepare by the method of example 1.2 using
20 3-cyano-3-(thiophen-2-yl)-pentanedioic acid diethyl ester (28 mmol), cobalt (II) chloride hexahydrate (55.5 mmol), and NaBH₄ (290 mmol). Chromatograph on silica gel to give the title compound.

25 53.3 Synthesis of 2-[3-(thiophen-2-yl)-pyrrolidin-3-yl]-
ethanol

Prepare by the method of example 1.3.2 using
30 [3-(thiophen-2-yl)-5-oxo-pyrrolidin-3-yl]-acetic acid ethyl ester (73 mmol). Chromatograph on silica gel to give the title compound.

35 53.4 Synthesis of 2-[3-(thiophen-2-yl)-1-(3,4,5-
trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethanol

Prepare by the method of example 3.1 using
2-[3-(thiophen-2-yl)-pyrrolidin-3-yl]-ethanol (23 mmol) and

3,4,5-trimethoxy-benzoyl chloride (23 mmol). Chromatograph on silica gel to give the title compound.

5 53.5 Synthesis of 2-[3-(thiophen-2-yl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate

Prepare by the method of example 3.2 using
10 2-[3-(thiophen-2-yl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethanol (8 mmol) and methanesulfonyl chloride (11 mmol) to give the title compound.

15 53.6 Synthesis of 1-[2-[3-(thiophen-2-yl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide

Prepare by the method of example 3.3 using 2-[3-(thiophen-2-yl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate (8 mmol) and 4-phenyl-piperidine-4-carboxylic acid amide hydrochloride (12 mmol).
20 Chromatograph on silica gel to give the title compound.

Example 54

25 Synthesis of 1-[2-[3-(pyridin-3-yl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide

30 54.1 Synthesis of 3-cyano-3-(pyridin-3-yl)-pentanedioic acid diethyl ester

Prepare by the method of example 1.1.2 using pyridin-3-yl-acetonitrile (0.161 mol) and ethyl bromoacetate (0.325
35 mol). Chromatograph on silica gel to give the title compound.

54.2 Synthesis of [3-(pyridin-3-yl)-5-oxo-pyrrolidin-3-yl]-acetic acid ethyl ester

5 Prepare by the method of example 1.2.2 using 3-cyano-3-(pyridin-3-yl)-pentanedioic acid diethyl ester (89 mmol). Chromatograph on silica gel to give the title compound.

10 54.3 Synthesis of 2-[3-(pyridin-3-yl)-pyrrolidin-3-yl]-ethanol

15 Prepare by the method of example 1.3.2 using [3-(pyridin-3-yl)-5-oxo-pyrrolidin-3-yl]-acetic acid ethyl ester (73 mmol). Chromatograph on silica gel to give the title compound.

54.4 Synthesis of 2-[3-(pyridin-3-yl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethanol

20 Prepare by the method of example 3.1 using 2-[3-(pyridin-3-yl)-pyrrolidin-3-yl]-ethanol (23 mmol) and 3,4,5-trimethoxy-benzoyl chloride (23 mmol). Chromatograph on silica gel to give the title compound.

25 54.5 2-[3-(pyridin-3-yl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate

30 Prepare by the method of example 3.2 using 2-[3-(pyridin-3-yl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethanol (8 mmol) and methanesulfonyl chloride (11 mmol) to give the title compound.

35 54.6 Synthesis of 1-[2-[3-(pyridin-3-yl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide

Prepare by the method of example 3.3 using 2-[3-(pyridin-3-yl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate (8 mmol) and 4-phenyl-

piperidine-4-carboxylic acid amide hydrochloride (12 mmol).
Chromatograph on silica gel to give the title compound.

5

Example 55

Synthesis of 1-[2-[3-(2-fluoro-phenyl)-1-(3,4,5-trimethoxy-
benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-
carboxylic acid amide

10

55.1 Synthesis of 3-cyano-3-(2-fluoro-phenyl)-
pentanedioic acid diethyl ester

Prepare by the method of example 1.1.2 using 2-
15 fluorophenylacetonitrile (0.161 mol) and ethyl bromoacetate
(0.325 mol). Chromatograph on silica gel to give the title
compound.

55.2 Synthesis of [3-(2-fluoro-phenyl)-5-oxo-pyrrolidin-
20 3-yl]-acetic acid ethyl ester

Prepare by the method of example 1.2.2 using 3-cyano-3-
(2-fluoro-phenyl)-pentanedioic acid diethyl ester (89
mmol). Chromatograph on silica gel to give the title
25 compound.

55.3 Synthesis of 2-[3-(2-fluoro-phenyl)-pyrrolidin-3-
yl]-ethanol

30 Prepare by the method of example 1.3.2 using [3-(2-
fluoro-phenyl)-5-oxo-pyrrolidin-3-yl]-acetic acid ethyl
ester (73 mmol). Chromatograph on silica gel to give the
title compound.

35 55.4 Synthesis of 2-[3-(2-fluoro-phenyl)-1-(3,4,5-
trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethanol

Prepare by the method of example 3.1 using 2-[3-(2-fluoro-phenyl)-pyrrolidin-3-yl]-ethanol (23 mmol) and 3,4,5-trimethoxy-benzoyl chloride (23 mmol). Chromatograph on silica gel to give the title compound.

55.5 Synthesis of 2-[3-(2-fluoro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate

10

Prepare by the method of example 3.2 using 2-[3-(2-fluoro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethanol (8 mmol) and methanesulfonyl chloride (11 mmol) to give the title compound.

15 55.6 Synthesis of 1-[2-[3-(2-fluoro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide

Prepare by the method of example 3.3 using 2-[3-(2-fluoro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate (8 mmol) and 4-phenyl-piperidine-4-carboxylic acid amide hydrochloride (12 mmol). Chromatograph on silica gel to give the title compound.

25

Example 56

30 Synthesis of 1-[2-[3-(4-hydroxy-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide

56.1 Synthesis of 4-(tert-butyldimethylsilyloxy)-phenyl-acetonitrile

35 Combine *tert*-butyldimethylsilyl chloride (0.460 mol), imidazole (0.600 mol) and DMF (125 mL). Add 4-hydroxyphenylacetonitrile (0.400 mol) and maintain at ambient temperature for 16 h. Dilute with ether (500 mL),

extract with water (4 X 75 mL), saturated sodium chloride (75 mL), dry over MgSO₄, filter, and concentrate *in vacuo* to obtain a residue. Chromatograph on silica gel to obtain the title compound.

56.2 Synthesis of 3-cyano-3-[4-(*tert*-butyldimethylsilyloxy)-phenyl]-pentanedioic acid diethyl ester

Prepare by the method of example 1.1.2 using 4-(*tert*-butyldimethylsilyloxy)-phenyl-acetonitrile (0.161 mol) and ethyl bromoacetate (0.325 mol). Chromatograph on silica gel to give the title compound.

56.3 Synthesis of [3-[4-(*tert*-butyldimethylsilyloxy)-phenyl]-5-oxo-pyrrolidin-3-yl]-acetic acid ethyl ester

Prepare by the method of example 1.2.2 using 3-cyano-3-[4-(*tert*-butyldimethylsilyloxy)-phenyl]-pentanedioic acid diethyl ester (89 mmol). Chromatograph on silica gel to give the title compound.

56.4 Synthesis of 2-[3-[4-(*tert*-butyldimethylsilyloxy)-phenyl]-5-oxo-pyrrolidin-3-yl]-ethanol

Prepare by the method of example 1.3.2 using [3-[4-(*tert*-butyldimethylsilyloxy)-phenyl]-5-oxo-pyrrolidin-3-yl]-acetic acid ethyl ester (73 mmol). Chromatograph on silica gel to give the title compound.

56.5 Synthesis of 2-[3-[4-(*tert*-butyldimethylsilyloxy)-phenyl]-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethanol

Prepare by the method of example 3.1 using 2-[3-[4-(*tert*-butyldimethylsilyloxy)-phenyl]-5-oxo-pyrrolidin-3-yl]-ethanol (23 mmol) and 3,4,5-trimethoxy-

benzoyl chloride (23 mmol). Chromatograph on silica gel to give the title compound.

5 56.6 Synthesis of 2-[3-[4-(*tert*-butyldimethylsilyloxy)-phenyl]-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate

Prepare by the method of example 3.2 using

10 2-[3-[4-(*tert*-butyldimethylsilyloxy)-phenyl]-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethanol (8 mmol) and methanesulfonyl chloride (11 mmol) to give the title compound.

15 56.7 Synthesis of 1-[2-[3-[4-(*tert*-butyldimethylsilyloxy)-phenyl]-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide

20 Prepare by the method of example 3.3 using 2-[3-[4-(*tert*-butyldimethylsilyloxy)-phenyl]-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate (8 mmol) and 4-phenyl-piperidine-4-carboxylic acid amide hydrochloride (12 mmol). Chromatograph on silica gel to
25 give the title compound.

56.8 Synthesis of 1-[2-[3-(4-hydroxy-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide

30

Combine 1-[2-[3-[4-(*tert*-butyldimethylsilyloxy)-phenyl]-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide (6 mmol) and THF (20 mL). Cool using an ice bath. Add a 1 M THF solution
35 of tetrabutylammonium fluoride (7 mL) in dropwise fashion. After 30 minutes, concentrate *in vacuo* to obtain a residue. Add dichloromethane (50 mL) to the residue. Extract with water (3 X 15 mL), dry over Na₂SO₄, filter, and concentrate

in vacuo to obtain a residue. Purify to obtain the title compound.

5

Example 57

Synthesis of 1-[2-[3-(4-trifluoromethyl-phenyl)-1-(3-isopropoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide

10

57.1 Synthesis of 3-cyano-3-(4-trifluoromethyl-phenyl)-pentanedioic acid diethyl ester

Prepare by the method of example 1.1.2 using 4-trifluoromethyl-phenylacetonitrile (0.161 mol) and ethyl bromoacetate (0.325 mol). Chromatograph on silica gel to give the title compound.

20

57.2 Synthesis of [3-(4-trifluoromethyl-phenyl)-5-oxo-pyrrolidin-3-yl]-acetic acid ethyl ester

Prepare by the method of example 1.2.2 using 3-cyano-3-(4-trifluoromethyl-phenyl)-pentanedioic acid diethyl ester (89 mmol). Chromatograph on silica gel to give the title compound.

57.3 Synthesis of 2-[3-(4-trifluoromethyl-phenyl)-pyrrolidin-3-yl]-ethanol

Prepare by the method of example 1.3.2 using [3-(4-trifluoromethyl-phenyl)-5-oxo-pyrrolidin-3-yl]-acetic acid ethyl ester (73 mmol). Chromatograph on silica gel to give the title compound.

57.4 Synthesis of 3-isopropoxybenzoic acid

Combine 3-hydroxybenzoic acid (100 mmol), 2-iodopropane (500 mmol), K₂CO₃ (300 mmol), and 2-butanone (300 mL).

Heat at reflux for 72 h. Concentrate *in vacuo* to obtain a residue. Add water (500 mL) and cool in an ice bath.

Adjust to pH 1 by dropwise addition of concentrated HCl.

- 5 Extract with dichloromethane (3 X 200 mL). Extract the combined organic layers with water (200 mL), dry over Na₂SO₄, filter, and concentrate *in vacuo* to obtain a residue. Purify to obtain the title compound.

10 57.5 Synthesis of 3-isopropoxy-benzoyl chloride

- Combine 3-isopropoxybenzoic acid (50 mmol) and dichloromethane (100 mL). Cool in an ice bath. Add in dropwise fashion, oxalyl chloride (55 mmol). Allow the
15 reaction mixture to warm to ambient temperature. After 2 h, concentrate *in vacuo* to obtain a residue. Use the title compound without further purification.

20 57.6 Synthesis of 2-[3-(4-trifluoromethyl-phenyl)-1-(3-isopropoxy-benzoyl)-pyrrolidin-3-yl]-ethanol

- Prepare by the method of example 3.1 using
2-[3-(4-trifluoromethyl-phenyl)-pyrrolidin-3-yl]-ethanol
(23 mmol) and 3-isopropoxy-benzoyl chloride (23 mmol).
25 Chromatograph on silica gel to give the title compound.

57.7 Synthesis of 2-[3-(4-trifluoromethyl-phenyl)-1-(3-isopropoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-bromide

- 30 Combine 2-[3-(4-trifluoromethyl-phenyl)-1-(3-isopropoxy-benzoyl)-pyrrolidin-3-yl]-ethanol (10 mmol), carbon tetrabromide (12.5 mmol), and dichloromethane (15 mL). Cool in an ice bath. Add in portions, triphenylphosphine (15 mmol). After 1 h, concentrate *in vacuo* to obtain a residue. Purify to obtain the title
35 compound.

57.8 Synthesis of 1-[2-[3-(4-trifluoromethyl-phenyl)-1-(3-isopropoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide

5

Combine 2-[3-(4-trifluoromethyl-phenyl)-1-(3-isopropoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-bromide (8 mmol), 4-phenyl-piperidine-4-carboxylic acid amide hydrochloride (12 mmol), K₂CO₃ (36 mmol), KI (0.8 mmol), and THF/H₂O (3/1, 80 mL). Heat at reflux for 72 h. Concentrate *in vacuo* to remove THF and extract with dichloromethane (2 X 50 mL). Extract the combined organic layers using water (50 mL). Dry over MgSO₄, filter, and concentrate *in vacuo* to obtain a residue. Chromatograph on silica gel to obtain the title compound.

Example 58

20 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-(thiophen-2-yl)-piperidine-4-carboxylic acid amide

58.1 Synthesis of 1-tert-butoxycarbonyl-4-cyano-4-(thiophen-2-yl)-piperidine

25

Prepare by the method of example 30.2 using 2-thiopheneacetonitrile (10 mmol) and 2-chloro-N-(2-chloroethyl)-N-tert-Butoxycarbonyl-ethanamine (11 mmol). Purify to give the title compound.

30

58.2 Synthesis of 4-cyano-4-(thiophen-2-yl)-piperidine hydrochloride

Prepare by the method of example 30.3 using 1-tert-butoxycarbonyl-4-cyano-4-(thiophen-2-yl)-piperidine (3 mmol) and HCl in dioxane (4N, 40 mmol). Concentrate the solvent *in vacuo* and dry under high vacuum to give the title compound.

58.3 Synthesis of 4-(thiophen-2-yl)-piperidine-4-carboxylic acid hydrochloride

5

Prepare by the method of example 20.6 using 4-cyano-4-(thiophen-2-yl)-piperidine hydrochloride (10 mmol) and KOH (0.4 mol, 3N). Purify to give the title compound.

10 58.4 Synthesis of 1-tert-butoxycarbonyl-4-(thiophen-2-yl)-piperidine-4-carboxylic acid

Prepare by the method of example 20.7 using 4-(thiophen-2-yl)-piperidine-4-carboxylic acid hydrochloride (10 mmol) and di-tert-butyl dicarbonate (11 mmol). Purify to give the title compound.

58.5 Synthesis of 1-tert-butoxycarbonyl-4-(thiophen-2-yl)-piperidine-4-carboxylic acid amide

20

Prepare by the method of example 20.8 using 1-tert-butoxycarbonyl-4-(thiophen-2-yl)-piperidine-4-carboxylic acid (4.0 mmol) and NH₃(gas). Purify to give the title compound.

25

58.6 Synthesis of 4-(thiophen-2-yl)-piperidine-4-carboxylic acid amide hydrochloride

Prepare by the method of example 20.10 using 1-tert-butoxycarbonyl-4-(thiophen-2-yl)-piperidine-4-carboxylic acid amide (3 mmol) and HCl in dioxane (40 mmol, 4N) to give the title compound.

58.7 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-(thiophen-2-yl)-piperidine-4-carboxylic acid amide

35

Prepare by the method of example 3.3 using 2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate (5 mmol) and 4-(thiophen-2-yl)-piperidine-4-carboxylic acid amide hydrochloride (7.5 mmol, 1.5 eq.). Chromatograph on silica gel to give the title compound.

Example 59

10

Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-5-oxo-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide

15 59.1 Synthesis of 4-(3,4-dichloro-phenyl)-4-[2-(tetrahydro-pyran-2-yloxy)-ethyl]-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-2-one

Combine 4-(3,4-dichloro-phenyl)-4-[2-(tetrahydro-pyran-2-yloxy)ethyl]-pyrrolidin-2-one (as prepared in example 11.3) (5 mmol) and 3,4,5-trimethoxy-benzoyl chloride (5.0 mmol) in N,N-dimethylaniline (20 mL). Heat to 90°C and stir for 24 h. Concentrate in vacuo. Partition the reaction mixture between dichloromethane and H₂O. Separate the organic layer, dry over MgSO₄, filter, and concentrate *in vacuo* to obtain a residue. Purify to give the title compound.

30 59.2 Synthesis of 4-(3,4-dichloro-phenyl)-4-(2-hydroxy-ethyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-2-one

Prepare according to the method of example 11.5 using 4-(3,4-dichloro-phenyl)-4-[2-(tetrahydro-pyran-2-yloxy)-ethyl]-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-2-one (3 mmol) and *p*-toluenesulfonic acid (200 mg). Chromatograph on silica gel to give the title compound.

59.3 Synthesis of 2-[3-(3,4-dichloro-phenyl)-5-oxo-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate

5

Prepare according to the method of example 3.2 using 4-(3,4-dichloro-phenyl)-4-(2-hydroxy-ethyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-2-one (5 mmol) and methanesulfonyl chloride (6 mmol). Dry under high vacuum at ambient temperature for 18 h to give the title compound.

10

59.4 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-5-oxo-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide

15

Prepare according to the method of example 3.3 using 2-[3-(3,4-dichloro-phenyl)-5-oxo-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl-methanesulfonate (5 mmol) and 4-phenyl-piperidine-4-carboxylic acid amide hydrochloride (7.5 mmol, 1.5 eq.). Chromatograph on silica gel to give the title compound.

20

Example 60

25 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide

60.1 Synthesis of 4-(3,4-dichloro-phenyl)-4-[2-(tetrahydro-pyran-2-yloxy)-ethyl]-pyrrolidine

30

Prepare according to the method of example 1.3.2 using 4-(3,4-dichloro-phenyl)-4-[2-(tetrahydro-pyran-2-yloxy)ethyl]-pyrrolidin-2-one (as prepared in example 11.3) (3 mmol), LiAlH₄ (18 mmol) H₂SO₄ (99.999%) (9 mmol). Purify to give the title compound.

35

60.2 Synthesis of 4-(3,4-dichloro-phenyl)-4-[2-
 (tetrahydro-pyran-2-yloxy)-ethyl]-1-(3,4,5-
 trimethoxy-benzyl)-pyrrolidine

5

Combine 4-(3,4-dichloro-phenyl)-4-[2-(tetrahydro-pyran-2-yloxy)-ethyl]-pyrrolidine (10 mmol), K₂CO₃ (30 mmol), and 3,4,5-trimethoxy-benzyl bromide (10 mmol) in THF/H₂O (4/1, 200 mL). Heat to reflux and stir for 16 h. Concentrate *in vacuo* to obtain a residue. Dilute the residue with ethyl acetate and extract with H₂O. Separate the layers, dry the organic layer over MgSO₄, filter, and concentrate *in vacuo*. Chromatograph on silica gel to give the title compound.

15 60.3 Synthesis of 4-(3,4-dichloro-phenyl)-4-2-hydroxy-
 ethyl-1-(3,4,5-trimethoxy-benzyl)-pyrrolidine

Prepare according to the method of example (11.5) using 4-(3,4-dichloro-phenyl)-4-[2-(tetrahydro-pyran-2-yloxy)-ethyl]-1-(3,4,5-trimethoxy-benzyl)-pyrrolidine (3 mmol) and p-toluenesulfonic acid (200 mg). Chromatograph on silica gel to give the title compound.

25 60.4 Synthesis of 2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-
 trimethoxy-benzyl)-pyrrolidin-3-yl]-ethyl-bromide

Prepare according to the method of example 57.7 using 4-(3,4-dichloro-phenyl)-4-2-hydroxy-ethyl-1-(3,4,5-trimethoxy-benzyl)-pyrrolidine (5 mmol), carbon tetrabromide (6.3 mmol), and triphenylphosphine (7.5 mmol). Purify to obtain the title compound.

35 60.5 Synthesis of 1-[2-[3-(3,4-dichloro-phenyl)-1-
 (3,4,5-trimethoxy-benzyl)-pyrrolidin-3-yl]-ethyl]-
 4-phenyl-piperidine-4-carboxylic acid amide

Prepare according to the method of example 57.8 using 2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzyl)-

pyrrolidin-3-yl]-ethyl-bromide (5 mmol) and 4-phenyl-piperidine-4-carboxylic acid amide hydrochloride (7.5 mmol, 1.5 eq.). Chromatograph on silica gel to give the title compound.

Example 61

Synthesis of 1-[3-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-propyl]-4-phenyl-piperidine-4-carboxylic acid amide

61.1 Synthesis of 2-(3,4-dichloro-phenyl)-5-(tetrahydro-pyran-2-yloxy)-pentanenitrile

Prepare according to the method of example 11.1 using 3,4-dichlorophenylacetonitrile (50 mmol) and 2-(3-bromopropoxy)-tetrahydro-pyran (50 mmol). Chromatograph on silica gel to give the title compound.

20

61.2 Synthesis of ethyl-[3-cyano-3-(3,4-dichloro-phenyl)-6-(tetrahydro-pyran-2-yloxy)]-hexanoate

Prepare according to the method of example 11.2 using 2-(3,4-dichloro-phenyl)-5-(tetrahydro-pyran-2-yloxy)-pentane nitrile (34 mmol) and ethyl bromoacetate (38 mmol, 1.1 eq.). Chromatograph on silica gel to give the title compound.

30

61.3 Synthesis of 4-(3,4-dichloro-phenyl)-4-[3-(tetrahydro-pyran-2-yloxy)-propyl]-pyrrolidin-2-one

Prepare according to the method of example 11.3 using ethyl-[3-cyano-3-(3,4-dichloro-phenyl)-6-(tetrahydro-pyran-2-yloxy)]-hexanoate (24 mmol) and Raney nickel (30 g). Chromatograph on silica gel to give the title compound.

35

61.4 Synthesis of 4-(3,4-dichloro-phenyl)-4-[3-(tetrahydro-pyran-2-yloxy)-propyl]-pyrrolidine

5 Prepare according to the method of example 1.3.2 using 4-(3,4-dichloro-phenyl)-4-[3-(tetrahydro-pyran-2-yloxy)-propyl]-pyrrolidin-2-one (3 mmol), LiAlH₄ (18 mmol) H₂SO₄ (99.999%) (9 mmol). Purify to give the title compound.

10 61.5 Synthesis of 4-(3,4-dichloro-phenyl)-4-[3-(tetrahydro-pyran-2-yloxy)-propyl]-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidine

15 Prepare by the method of example 3.1 using 4-(3,4-dichloro-phenyl)-4-[3-(tetrahydro-pyran-2-yloxy)-propyl]-pyrrolidine (2 mmol) and 3,4,5-trimethoxy-benzoyl chloride (2 mmol). Chromatograph on silica gel to give the title compound.

20 61.6 Synthesis of 4-(3,4-dichloro-phenyl)-4-(3-hydroxy-propyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidine

25 Prepare according to the method of example 11.5 using 4-(3,4-dichloro-phenyl)-4-[3-(tetrahydro-pyran-2-yloxy)-propyl]-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidine (3 mmol) and p-toluenesulfonic acid (200 mg). Chromatograph on silica gel to give the title compound.

30 61.7 Synthesis of 3-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-propyl-methanesulfonate

35 Prepare according to the method of example 3.2 using 4-(3,4-dichloro-phenyl)-4-(3-hydroxy-propyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidine (5 mmol) and methanesulfonyl chloride (6 mmol). Dry under high vacuum at ambient temperature for 18 h to give the title compound.

61.8 Synthesis of 1-[3-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-propyl]-4-phenyl-piperidine-4-carboxylic acid amide

5

Prepare according to the method of example 3.3 using 3-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-propyl-methanesulfonate (5 mmol) and 4-phenyl-piperidine-4-carboxylic acid amide hydrochloride (7.5 mmol, 1.5 eq.). Chromatograph on silica gel to give the title compound.

Example 62

15 Synthesis of 1-[3-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzyl)-pyrrolidin-3-yl]-propyl]-4-phenyl-piperidine-4-carboxylic acid amide

20 62.1 Synthesis of 4-(3,4-dichloro-phenyl)-4-[3-(tetrahydro-pyran-2-yloxy)-propyl]-1-(3,4,5-trimethoxy-benzyl)-pyrrolidine

Combine 4-(3,4-dichloro-phenyl)-4-[3-(tetrahydro-pyran-2-yloxy)-propyl]-pyrrolidine (10 mmol), K₂CO₃ (30 mmol), and 3,4,5-trimethoxy-benzyl bromide (10 mmol) in THF/H₂O (4/1, 200 mL). Heat to reflux and stir for 16 h. Concentrate *in vacuo* to obtain a residue. Dilute the residue with ethyl acetate and extract with H₂O. Separate the layers, dry the organic layer over MgSO₄, filter, and concentrate *in vacuo*. Chromatograph on silica gel to give the title compound.

62.2 Synthesis of 4-(3,4-dichloro-phenyl)-4-(3-hydroxy-propyl)-1-(3,4,5-trimethoxy-benzyl)-pyrrolidine

35 Prepare according to the method of example 11.5 using 4-(3,4-dichloro-phenyl)-4-[3-(tetrahydro-pyran-2-yloxy)-propyl]-1-(3,4,5-trimethoxy-benzyl)-pyrrolidine (3 mmol)

and p-toluenesulfonic acid (200 mg). Chromatograph on silica gel to give the title compound.

5 62.3 Synthesis of 3-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzyl)-pyrrolidin-3-yl]-propyl-bromide

Prepare according to the method of example 57.7 using 4-(3,4-dichloro-phenyl)-4-(3-hydroxy-propyl)-1-(3,4,5-trimethoxy-benzyl)-pyrrolidine (5 mmol), carbon tetrabromide (6.3 mmol), and triphenylphosphine (7.5 mmol). Purify to obtain the title compound.

15 62.4 Synthesis of 1-[3-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzyl)-pyrrolidin-3-yl]-propyl]-4-phenyl-piperidine-4-carboxylic acid amide

Prepare according to the method of example 57.8 using 3-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzyl)-pyrrolidin-3-yl]-propyl-bromide (5 mmol) and 4-phenyl-piperidine-4-carboxylic acid amide hydrochloride (7.5 mmol, 1.5 eq.). Chromatograph on silica gel to give the title compound.

25 **Example 63**

Synthesis of 1-[3-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzyl)-5-oxo-pyrrolidin-3-yl]-propyl]-4-phenyl-piperidine-4-carboxylic acid amide

30

63.1 Synthesis of 4-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzyl)-4-[3-(tetrahydro-pyran-2-yloxy)-propyl]-pyrrolidin-2-one

35 Prepare according to the procedure of example 11.4 using 4-(3,4-dichloro-phenyl)-4-[3-(tetrahydro-pyran-2-yloxy)-propyl]-pyrrolidin-2-one (2.79 mmol) and 3,4,5-

trimethoxy-benzyl bromide (5.9 mmol). Chromatograph on silica gel to give the title compound.

5 63.2 Synthesis of 4-(3,4-dichloro-phenyl)-4-(3-hydroxy-propyl)-1-(3,4,5-trimethoxy-benzyl)-pyrrolidin-2-one

Prepare according to the method of example 11.5 using
10 4-(3,4-dichloro-phenyl)-4-[3-(tetrahydro-pyran-2-yloxy)-propyl]-1-(3,4,5-trimethoxy-benzyl)-pyrrolidin-2-one (3 mmol) and p-toluenesulfonic acid (200 mg). Chromatograph on silica gel to give the title compound.

15 63.3 Synthesis of 3-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzyl)-5-oxo-pyrrolidin-3-yl]-propyl-methanesulfonate

Prepare according to the method of example 3.2 using 4-
20 (3,4-dichloro-phenyl)-4-(3-hydroxy-propyl)-1-(3,4,5-trimethoxy-benzyl)-pyrrolidin-2-one (5 mmol) and methanesulfonyl chloride (6 mmol). Dry under high vacuum at ambient temperature for 18 h to give the title compound.

25 63.4 Synthesis of 1-[3-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzyl)-5-oxo-pyrrolidin-3-yl]-propyl]-4-phenyl-piperidine-4-carboxylic acid amide

Prepare according to the method of example 3.3 using 3-
30 [3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzyl)-5-oxo-pyrrolidin-3-yl]-propyl-methanesulfonate (5 mmol) and 4-phenyl-piperidine-4-carboxylic acid amide hydrochloride (7.5 mmol, 1.5 eq.). Chromatograph on silica gel to give the title compound.

35

Synthesis of 1-[3-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-5-oxo-pyrrolidin-3-yl]-propyl]-4-phenyl-piperidine-4-carboxylic acid amide

5

64.1 Synthesis of 4-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-4-[3-(tetrahydro-pyran-2-yloxy)-propyl]-pyrrolidin-2-one

10 Prepare according to the procedure of example 59.1 using 4-(3,4-dichloro-phenyl)-4-[3-(tetrahydro-pyran-2-yloxy)-propyl]-pyrrolidin-2-one (5.0 mmol) and 3,4,5-trimethoxy-benzoyl chloride (5.0 mmol). Chromatograph on silica gel to give the title compound.

15

64.2 Synthesis of 4-(3,4-Dichloro-phenyl)-4-(3-hydroxy-propyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-2-one

20 Prepare according to the method of example 11.5 using 4-(3,4-dichloro-phenyl)-4-[3-(tetrahydro-pyran-2-yloxy)-propyl]-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-2-one (3 mmol) and p-toluenesulfonic acid (200 mg). Chromatograph on silica gel to give the title compound.

25

64.3 Synthesis of 3-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-5-oxo-pyrrolidin-3-yl]-propyl-methanesulfonate

30 Prepare according to the method of example 3.2 using 4-(3,4-dichloro-phenyl)-4-(3-hydroxy-propyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-2-one (5 mmol) and methanesulfonyl chloride (6 mmol). Dry under high vacuum at ambient temperature for 18 h to give the title compound.

35

64.4 Synthesis of 1-[3-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-5-oxo-pyrrolidin-3-yl]-propyl]-4-phenyl-piperidine-4-carboxylic acid amide

Prepare according to the method of example 3.3 using
3-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-5-
5 oxo-pyrrolidin-3-yl]-propyl-methanesulfonate (5 mmol) and
4-phenyl-piperidine-4-carboxylic acid amide hydrochloride
(7.5 mmol, 1.5 eq.). Chromatograph on silica gel to give
the title compound.

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The compounds of the present invention are useful in their pharmacological activities such as tachykinin antagonism, especially substance P and neurokinin A antagonism, and the like. One object of the present invention is to provide new and useful antagonists of tachykinins, especially substance P and neurokinin A. A particular object of the present invention are those compounds that exhibit both NK₁ and NK₂ receptor antagonism. For some compounds, significant antagonism of NK₃ receptors may additionally be useful.

The compounds of the present invention are believed to exert their therapeutic effect through antagonism of NK₁ and NK₂ receptors and thereby provide relief for diseases and conditions associated with inflammation, pain, and the central nervous system. However, it is understood that the present invention is not limited by any particular theory or proposed mechanism to explain its effectiveness in an end-use application.

A further object of the present invention is to provide compounds, stereoisomers, or pharmaceutically acceptable salts thereof, for the treatment and prevention of various diseases in a patient in need thereof. Because the compounds of the present invention are tachykinin antagonists, they are potentially useful in the treatment of conditions associated with inflammation, including asthma, allergies, bronchitis, rhinitis, Crohn's disease, ulcerative colitis, rheumatoid arthritis, osteoarthritis, migraine, cystitis and hypersensitivity reactions. Tachykinin antagonism may also be appropriate therapy for the treatment of cough, emesis, pain, peripheral neuropathy, post-herpetic neuralgia, adverse immunological reactions, blood flow disorders due to vasodilation, ophthalmic diseases, such as conjunctivitis and cutaneous diseases such as contact dermatitis, atopic dermatitis,

urticaria and the like. Various central nervous system disorders including anxiety, depression, psychosis, schizophrenia and dementia may also be amenable to
5 treatment with tachykinin antagonists.

The compounds of formula (1) are believed to exert their inhibitory effect through antagonism of NK₁ and NK₂ receptors and thereby provide relief for neurogenic
10 inflammatory diseases including but not limited to asthma and other inflammatory conditions of the lung. Additionally, compounds of the present invention are also believed to be useful for conditions associated with rhinitis, cough, and pain.

15 Various diseases and conditions described to be treated herein, are well known and appreciated by those skilled in the art. It is also recognized that one skilled in the art may affect the associated diseases and conditions by
20 treating a patient presently afflicted with the diseases or conditions or by prophylactically treating a patient afflicted with the diseases or conditions with a therapeutically effective amount of the compounds of formula (1).

25 As used herein, the term "patient" refers to a warm blooded animal such as a mammal which is afflicted with a particular inflammatory disease state. It is understood that guinea pigs, dogs, cats, rats, mice, horses, cattle,
30 sheep, and humans are examples of animals within the scope of the meaning of the term.

As used herein, the term "therapeutically effective amount" of a compound of formula (1) refers to an amount
35 which is effective in controlling diseases and conditions associated with inflammation, pain, and the central nervous system. The term "controlling" is intended to refer to all processes wherein there may be a slowing, interrupting,

arresting, or stopping of the progression of the diseases and conditions described herein, but does not necessarily indicate a total elimination of all disease and condition symptoms, but does include prophylactic treatment of the diseases and conditions associated with inflammation, pain, and the central nervous system.

A therapeutically effective amount can be readily determined by the attending diagnostician, as one skilled in the art, by the use of conventional techniques and by observing results obtained under analogous circumstances. In determining the therapeutically effective amount, the dose, a number of factors are considered by the attending diagnostician, including, but not limited to: the species of mammal; its size, age, and general health; the specific disease involved; the degree of or involvement or the severity of the disease; the response of the individual patient; the particular compound administered; the mode of administration; the bioavailability characteristic of the preparation administered; the dose regimen selected; the use of concomitant medication; and other relevant circumstances.

A therapeutically effective amount of a compound of formula (1) is expected to vary from about 0.1 milligram per kilogram of body weight per day (mg/kg/day) to about 100 mg/kg/day. Preferred amounts are able to be determined by one skilled in the art.

30

In effecting treatment of a patient afflicted with the diseases and conditions described above, a compound of formula (1) can be administered in any form or mode which makes the compound bioavailable in a therapeutically effective amount, including oral, inhalation, and parenteral routes. For example, compounds of formula (1) can be administered orally, by inhalation of an aerosol or dry powder, subcutaneously, intramuscularly,

intravenously, transdermally, intranasally, rectally, topically, and the like. Oral or inhalation administration is generally preferred for treatment of
5 respiratory diseases, e.g. asthma. One skilled in the art of preparing formulations can readily select the proper form and mode of administration depending upon the particular characteristics of the compound selected, the disease or condition state to be treated, the stage of the
10 disease or condition, and other relevant circumstances. (Remington's Pharmaceutical Sciences, 18th Edition, Mack Publishing Co. (1990)).

The compounds of the present invention can be
15 administered alone or in the form of a pharmaceutical composition in combination with pharmaceutically acceptable carriers or excipients, the proportion and nature of which are determined by the solubility and chemical properties of the compound selected, the chosen
20 route of administration, and standard pharmaceutical practice. The compounds of the present invention, while effective themselves, may be formulated and administered in the form of their pharmaceutically acceptable salts, such as acid addition salts or base addition salts, for
25 purposes of stability, convenience of crystallization, increased solubility and the like.

In another embodiment, the present invention provides pharmaceutical compositions comprising a therapeutically
30 effective amount of a compound of formula (1) in admixture or otherwise in association with one or more pharmaceutically acceptable carriers or excipients.

The pharmaceutical compositions are prepared in a
35 manner well known in the pharmaceutical art. The carrier or excipient may be a solid, semi-solid, or liquid material which can serve as a vehicle or medium for the active ingredient. Suitable carriers or excipients are

well known in the art. The pharmaceutical composition may be adapted for oral, inhalation, parenteral, or topical use and may be administered to the patient in the form of
5 tablets, capsules, aerosols, inhalants, suppositories, solution, suspensions, or the like.

The compounds of the present invention may be administered orally, for example, with an inert diluent or
10 with an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the compounds may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups,
15 wafers, chewing gums and the like. These preparations should contain at least 4% of the compound of the present invention, the active ingredient, but may be varied depending upon the particular form and may conveniently be between 4% to about 70% of the weight of the unit. The
20 amount of the compound present in compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations according to the present invention may be determined by someone skilled in the art.

25 The tablets, pills, capsules, troches and the like may also contain one or more of the following adjuvants: binders such as microcrystalline cellulose, gum tragacanth or gelatin; excipients such as starch or lactose, disintegrating agents such as alginic acid, Primogel, corn starch
30 and the like; lubricants such as magnesium stearate or Sterotex; glidants such as colloidal silicon dioxide; and sweetening agents such as sucrose or saccharin may be added or a flavoring agent such as peppermint, methyl salicylate or orange flavoring. When the dosage unit form
35 is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as polyethylene glycol or a fatty oil. Other dosage unit forms may contain other various materials which modify the physical form of the dosage unit, for example, as coatings. Thus,

tablets or pills may be coated with sugar, shellac, or other enteric coating agents. A syrup may contain, in addition to the present compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

10 For the purpose of parenteral therapeutic administration, the compounds of the present invention may be incorporated into a solution or suspension. These preparations should contain at least 0.1% of a compound of the invention, but may be varied to be between 0.1 and
15 about 50% of the weight thereof. The amount of the compound of formula (1) present in such compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations are able to be determined by one skilled in the art.

20 The compounds of the present invention may also be administered by inhalation, such as by aerosol or dry powder. Delivery may be by a liquefied or compressed gas or by a suitable pump system which dispenses the the
25 compounds of the present invention or a formulation thereof. Formulations for administration by inhalation of compounds of formula (1) may be delivered in single phase, bi-phasic, or tri-phasic systems. A variety of systems are available for the administration by aerosols of the
30 compounds of formula (1). Dry powder formulations are prepared by either pelletizing or milling the compound of formula (1) to a suitable particle size or by admixing the pelletized or milled compound of formula (1) with a suitable carrier material, such as lactose and the like.
35 Delivery by inhalation includes the necessary container, activators, valves, subcontainers, and the like. Preferred aerosols and dry powder formulations for

administration by inhalation can be determined by one skilled in the art.

5 The compounds of the present invention may also be administered topically, and when done so the carrier may suitably comprise a solution, ointment or gel base. The base, for example, may comprise one or more of the following: petrolatum, lanolin, polyethylene glycols, bee
10 wax, mineral oil, diluents such as water and alcohol, and emulsifiers and stabilizers. Topical formulations may contain a concentration of the formula (1) or its pharmaceutical salt from about 0.1 to about 10% w/v (weight per unit volume).

15

 The solutions or suspensions may also include one or more of the following adjuvants: sterile diluents such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other
20 synthetic solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylene diaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the
25 adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in ampules, disposable syringes or multiple dose vials made of glass or plastic.

30

EXAMPLE 14

ANTAGONISM OF IODINATED TACHYKININ BINDING TO NK₁ AND NK₂ RECEPTORS BY PUTATIVE ANTAGONISTS

35 The NK₁ receptor affinity of proposed tachykinin antagonists was evaluated in guinea pig lungs (Keystone Biologicals, Cleveland, OH), affinity for the NK₂ receptor evaluated in HSKR-1 cells (which are mouse 3T3 fibroblasts

expressing the human jejunal NK₂ receptor) and NK-3 receptor affinity was evaluated in freshly collected guinea pig cerebral cortex. Tissues or cells were

5 homogenized with a Polytron in 15 volumes of 50 mM Tris-HCl buffer (pH 7.4, 4°C) and centrifuged. The pellet was resuspended in Tris-HCl buffer and was centrifuged; the pellet was washed twice by resuspension. The final pellet was resuspended at a concentration of 40 mg/ml for tissues

10 (guinea pig lung and cerebral cortex) and 20 mg/ml for cells in incubation buffer and remained at room temperature for at least 15 min prior to use. Receptor binding was initiated by addition of 250 ul membrane preparation in duplicate to 0.1 nM of the following

15 radioligands: ¹²⁵I-Bolton Hunter Lys-3 labeled substance P; ¹²⁵iodohistidyl-1-neurokinin A; and ¹²⁵I-Bolton Hunter labeled Lys-4 eledoisin in a final volume of 500 ul of buffer containing 50 mM Tris-HCl (pH 7.4 at room temperature), 0.1% bovine serum albumin, 2 mM MnCl₂, 40

20 ug/ml bacitracin, 4 µg/ml leupeptin and chymostatin, 1 µM thiorphan and various doses of the putative tachykinin antagonists. Incubations were performed at room temperature for 90 min (NK₁ receptor assays) or 2 hr (NK₂ and NK₃ receptor assays); binding was terminated by

25 addition of 50 mM Tris-HCl buffer (pH 7.4, 4°C) and filtration under vacuum through GF/B filters presoaked with 0.1% polyethyleneimine (NK₁ receptor assays) or 0.5% bovine serum albumin (NK₂ and NK₃ receptor assays). Filter bound radioactivity was quantitated in a gamma counter.

30 Nonspecific binding was defined as binding in the presence of 1 µM substance P, neurokinin A, or eledoisin. Specific binding was calculated by subtracting nonspecific binding from total binding. Competition of iodinated SP, NKA, or eledoisin binding by test compounds or standards was

35 expressed as a percentage of this maximum competition. IC₅₀ values (concentration required to inhibit 50% of receptor binding) were generated for each of the test

compounds by nonlinear regression using an iterative curve fitting program (GraphPAD Inplot, San Diego, CA).

5 IC_{50} values for the compounds in question are found in Table 2 and represent the mean of several experiments. Several of the compounds presented, e.g. Example 3 exhibits high affinity for both NK_1 , and NK_2 receptors as well as for NK_3 receptors.

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TABLE 2

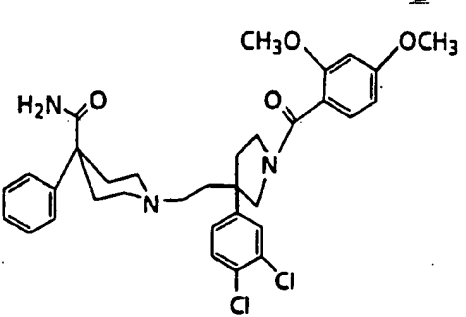
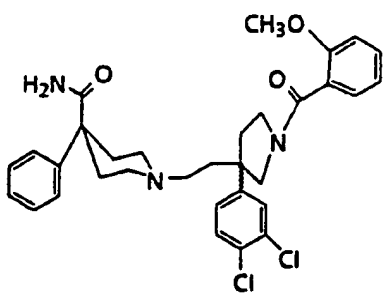
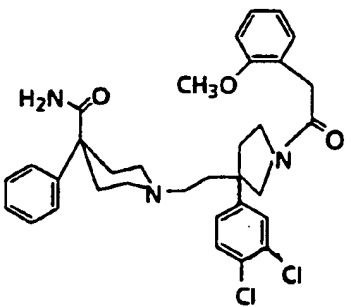
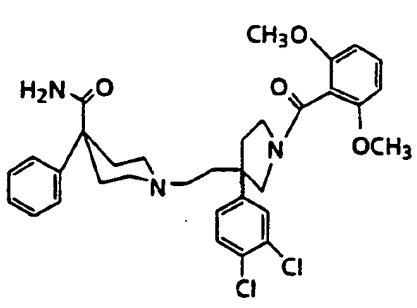
EXAMPLE	STRUCTURE	NK-2 IC ₅₀ (nM)	NK-1 IC ₅₀ (nM)	NK-3 IC ₅₀ (nM)
2		34	131	65
13		14	74	
4		74	48	41
5		41	20	65

TABLE 2 (cont'd)

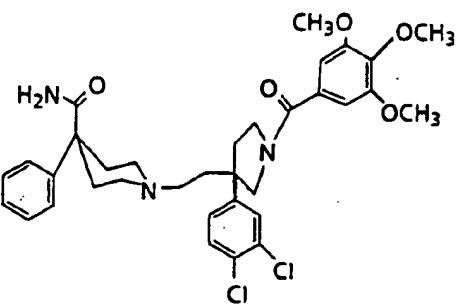
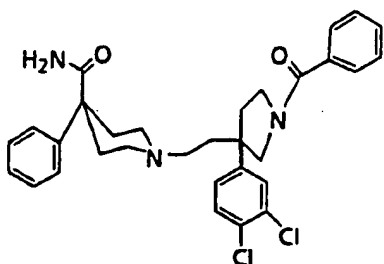
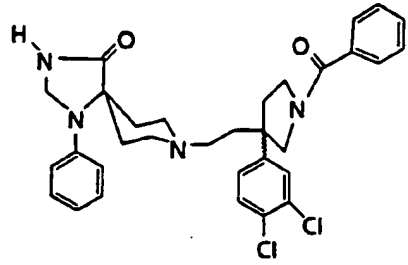
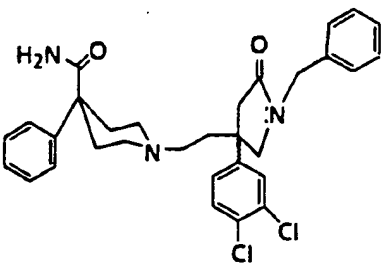
EXAMPLE	STRUCTURE	NK-2 IC ₅₀ (nM)	NK-1 IC ₅₀ (nM)	NK-3 IC ₅₀ (nM)
3		15	5	—
1		7	270	162
10		11	255	1191
11		127	196	203

TABLE 2 (cont'd)

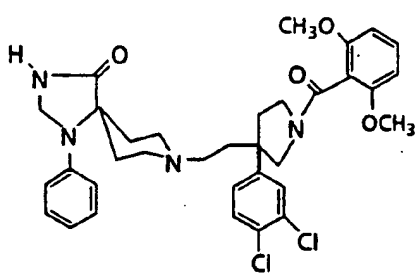
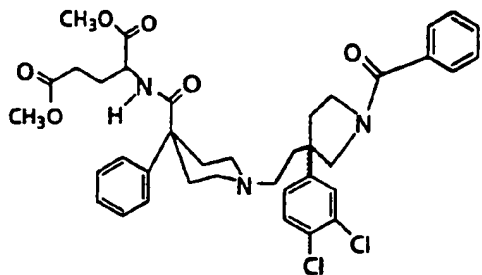
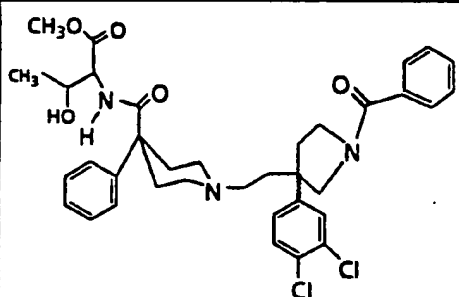
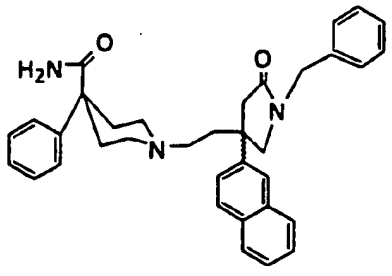
EXAMPLE	STRUCTURE	NK-2 IC ₅₀ (nM)	NK-1 IC ₅₀ (nM)	NK-3 IC ₅₀ (nM)
9		118	49	183
6		15	182	—
7		10	240	202
12		179	810	—

TABLE 2 (cont'd)

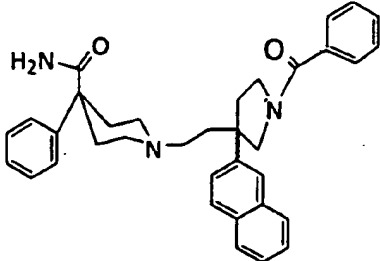
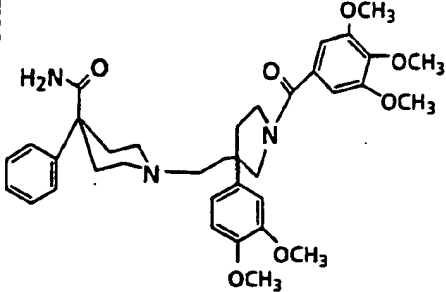
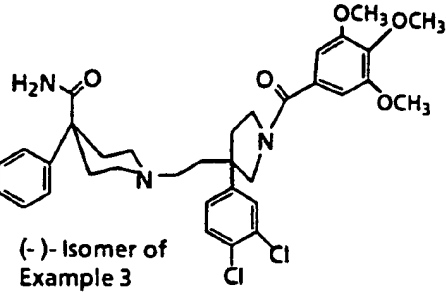
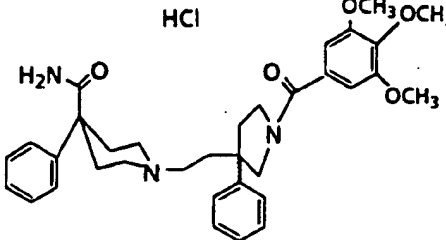
EXAMPLE	STRUCTURE	NK-2 IC ₅₀ (nM)	NK-1 IC ₅₀ (nM)	NK-3 IC ₅₀ (nM)
8		94	1480	—
23		2683	20.0	—
21	 (-)- Isomer of Example 3	760	183	2304
22A	 HCl	1187	17.4	—

TABLE 2 (cont'd)

EXAMPLE	STRUCTURE	NK-2 IC ₅₀ (nM)	NK-1 IC ₅₀ (nM)	NK-3 IC ₅₀ (nM)
20	<p>(+)- Isomer of Example 3</p>	8.40	4.65	21
20A	<p>(+)- Isomer of Example 3</p>	7.93	2.99	—
3A	<p>(+)- Isomer of Example 3</p>	21	5.97	54.2
5A	<p>(+)- Isomer of Example 3</p>	40	20	—

EXAMPLE 15

5

ANTAGONISM OF NK₁ AND NK₂ RECEPTOR MEDIATED
PHOSPHATIDYLINOSITOL TURNOVER

Tachykinin-mediated inositol phosphate accumulation
10 was measured in UCL1 or SKLKB82#3 cells in the presence
and absence of NK₁ or NK₂ receptor antagonists,
respectively. Tissues were incubated in Krebs-Henseleit
buffer at 37°C with 95% O₂-5% CO₂ gassing. Tissues were
then incubated with fresh buffer containing 100 µCi of
15 myo-[2-³H(N)] inositol at 37°C for 60 min with gentle
gassing. After washing twice in 5 ml room temperature
buffer containing 10 mM LiCl, tissues were incubated for
30 min at room temperature with a buffer change at 15 min.
Buffer was removed and Krebs-Henseleit buffer (containing
20 40 µg/ml bacitracin, 4 µg/ml each of leupeptin and
chymostatin, 0.1% bovine serum albumin and 10 mM each of
thiorphan and LiCl) added. After 15 min, SP was added to
UCL1 cells or NKA to SKLKB82#3 cells at various
concentrations to start the reaction. After incubation
25 for 60 min at room temperature the reaction was terminated
by addition of 930 µl chloroform:methanol (1:2 by volume)
to each tube, followed by 310 µl chloroform and 310 µl
doubly distilled water. Samples were vortexed,
centrifuged, and 0.9 ml of the aqueous (top) phase removed
30 and added to 2 ml ddH₂O. The mixture was vortexed and
loaded onto a 50% Bio-Rad AG 1-X8 (formate form, 100-200
mesh) exchange column (Bio-Rad Laboratories, Hercules,
CA). The columns were washed, in order, with: 1) 10 ml
doubly distilled water, 2) 5 ml of 5 mM disodium
35 tetraborate/60 mM sodium formate, and 3) 5 ml of 1 M
ammonium formate/0.1 M formic acid. The third elution was
collected and 1 ml counted in 7 ml scintillation fluid. A
50 µl aliquot of the organic (bottom) phase was removed,

dried in a scintillation vial and counted in 7 ml scintillation fluid.

5 The ratio of DPM in the aqueous phase aliquot (total inositol phosphates) to the DPM in the 50 μ l organic phase aliquot (total [3 H]inositol incorporated) was calculated for each sample. Data are expressed as a percent of agonist-induced accumulation of [3 H]-inositol phosphates
10 over basal levels. The ratios in the presence of test compound and/or standards were compared to the ratios for control samples (i.e. no stimulating agonist). Dose-response graphs were constructed and the abilities of the test compounds to inhibit tachykinin-induced
15 phosphatidylinositol turnover determined with the aid of a computer program. Figure 1 illustrates the ability of Example 3 to produce dose related antagonism of the receptor mediated SP or NKA induced PI turnover in UC11 (Figure 1a) or SKLKB82#3 cells (Figure 1b), respectively.
20 Data is expressed as percent stimulation of total inositol phosphate accumulation over basal levels and normalized to the maximum response produced by SP. These data suggest Example 3 has no agonist activity and antagonizes both NK₁ (on UC11 cells) and NK₂ (on SKLKB82#3) receptors in a dose-
25 dependent manner. Schild analysis is performed using dose response curves (such as those presented in Figures 1a and 1b) to obtain a value indicative of the strength of a competitive antagonist and is expressed as the pA₂, which is the negative logarithm of the molar concentration of
30 antagonist which reduces the effect of a dose of agonist to one-half of that expected at the dose of agonist. Table 3 contains data demonstrating the ability of the compounds of Example 3A; Example 5A; and Example 20 to functionally antagonize the effects of SP or NKA *in vitro*.
35 These compounds antagonized both NK₁ and NK₂ receptors by nearly equivalent amounts. It is further important to note that none of the compounds alone stimulated PI turnover suggesting an absence of agonist activity.

Table 3.
Apparent Affinities of Compounds for
Tachykinin Receptors

5	NK-1 RECEPTOR			NK-2 RECEPTOR	
	COMPOUND	pA ₂	-SLOPE	pA ₂	-SLOPE
	EXAMPLE 3A	7.91 (7.71-8.23)	0.90 (0.65-1.15)	8.75 (7.78-9.72)	0.73 (0.49-0.97)
	EXAMPLE 5A	7.32 (4.84-9.80)	1.17 (0.41-1.93)	7.35 (6.93-7.77)	1.11 (0.99-1.23)
10	EXAMPLE 20	8.19 (7.37-9.00)	1.03 (0.78-1.28)	8.67 (8.20-9.14)	1.00 (0.63-1.37)

Values are mean (95% confidence limits) derived from Schild analysis of 2-3 experiments per compound per receptor.

15

EXAMPLE 16

ANTAGONISM OF SP-INDUCED PLASMA PROTEIN EXTRAVASATION IN GUINEA PIG TRACHEA

20 SP-induced protein leakage through postcapillary
venules was assessed by measuring Evans Blue dye
accumulation in guinea pig trachea. Animals were
anesthetized with pentobarbital then injected with Evans
Blue dye (20 mg/kg, i.v., prepared in 0.9% NaCl solution).
25 One minute after dye administration, the antagonist was
administered (i.v.) followed by SP (0.3 nmole/kg, i.v.)
and, after 5 min, excess dye removed from the circulation
by transcardiac perfusion with 50 ml 0.9% NaCl solution.
The trachea and primary bronchi were removed, blotted dry
30 and weighed. Dye quantitation was performed
spectrophotometrically (620 nm) after extracting tissues
in formamide for 24 hr at 50°C. Values were subtracted
from background (dye only, no agonist). ED₅₀ (dose of
compound which inhibits SP-induced plasma protein
35 extravasation by 50%) was calculated from linear
regression analysis.

Figure 2 illustrates the ability of Example 3 to produce a dose related antagonism of SP-induced plasma protein extravasation in guinea pig trachea. These data suggest that Example 3 acts as an antagonist of NK₁ receptors *in vivo*.

Table 4, "Antagonism of SP-Induced Plasma Protein Extravasation in Guinea Pig Airways", contains data for the compound of Example 3 and its (+)-enantiomer the compound of Example 20A. These compounds are equipotent NK-1 receptor antagonists in this system.

Table 4.

Antagonism of SP-induced Plasma Protein Extravasation in Guinea Pig Trachea

COMPOUND	ED ₅₀ (mg/kg)
Example 3A	0.17(0.004-0.274)
Example 20A	0.20(0.004-0.31)

Values are mean (95% confidence limits). Compounds were injected intravenously 2 min prior to SP administration. ED₅₀ values are based on at least 3 doses; at least 4 animals were used per dose.

EXAMPLE 17

5 ANTAGONISM OF NKA AND CAPSAICIN INDUCED RESPIRATORY
 EFFECTS IN CONSCIOUS GUINEA PIGS

In vivo experiments were performed using male Duncan Hartley guinea pigs (250-350g). Changes in conscious breathing patterns were monitored in four animals simultaneously using modified whole body plethysmography consisting of four small plexiglass boxes each connected to a reference box via Validyne DP 45-16 differential pressure transducers. The 4 boxes were equipped with an air supply line (also used for aerosol delivery) and an exhaust air line. Supply and exhaust lines were of the same length and narrow bore and arose from a common supply chamber and vented to a common exhaust chamber. This system was used to ensure that fluctuations in supply air and atmospheric pressure would remain in phase and be eliminated from the net signal by the differential pressure transducers. The analog pressure signals were digitalized via a Data Translation DT2821 A to D board. Data were collected at a rate of 100 samples/second/animal. Each cycle of pressure change was analyzed using the following parameters: rising and falling slope determined between minimum and maximum pressures, the ratio of rising over falling slope, and the magnitude of the change between initial trough pressure and peak cycle pressure. Using these values (and observing the animals) the pressure cycles were characterized into normal breaths, forced exhalations (apparent by abdominal heaving), significant respiratory events (SREs; usually coughs, less often sneezes or gasps which were characterized by transient, extremely large pressure increases which were distinguishable from noise) and movement/noise with a PCAT 286 running a System V UNIX operating system. Dyspnea was defined as a significant,

sustained increase in plethysmograph pressure which was associated with an observable shift to labored breathing in the animal.

5

During the course of a typical experiment in which airway responsiveness to various bronchoconstricting agents was examined, aerosols were delivered for 19 min (0.33 ml/min) using a DeVilbiss Ultraneb 99 ultrasonic nebulizer and animals monitored during this time. Prior to nebulization, 1 min of resting breathing was collected to establish a baseline pressure. In preliminary experiments, various concentrations of the bronchoconstrictive agents were evaluated and the concentration chosen which maximized the number of animals exhibiting dyspnea but minimized the severity of the response. Hence, neurokinin A was delivered at a final concentration of 0.05%, and capsaicin, 0.001%. The vehicle for nebulization of all bronchoconstrictive agents was phosphate buffered saline (pH 7.4) which elicited no respiratory effects itself. Putative tachykinin antagonists were administered either (i.v.) 20 min prior to onset of aerosol exposure or orally 1 hour prior to onset (to guinea pigs after an overnight fast).

25

"Antagonism of NKA- Induced Respiratory Effects in Conscious Guinea Pigs"

Table 6 illustrates the effects of the compounds of Example 3; Example 20A; and Example 5A on respiratory effects induced by NKA aerosol. All compounds reduced the effects of NKA aerosol as suggested by a decrease in the number of animals exhibiting dyspnea in response to the tachykinin or an increase in the period of time (or amount of aerosol) required to elicit the dyspnea response. These effects were dose dependent i.e. the higher the dose of compound, the greater attenuation of NKA-mediated effects. These data indicate that these compounds are

capable of producing NK₂ receptor antagonism in guinea pigs *in vivo*.

5

Table 6.

Modulation of Respiratory Effects Produced by NKA Aerosol
in Conscious Guinea Pigs

	TREATMENT	DYSPNEA INCIDENCE	DYSPNEA ONSET (sec)
10	VEHICLE	100% (37/37)	397 ± 29.5
	Example 3		
	5 mg/kg	86% (6/7)	394 ± 32
15	10 mg/kg	60% (6/10)	801 ± 104
	Example 20A		
	1 mg/kg	100% (10/10)	451 ± 30
	5 mg/kg	90% (9/10)	706 ± 82
20	10 mg/kg	70% (7/10)	829 ± 105
	Example 5A		
	5 mg/kg	60% (3/5)	654 ± 37
	10 mg/kg	54% (7/13)	608 ± 65

25

Compounds were administered 20 min prior to initiation of NKA aerosol (0.05%). Values for each treatment represent the mean and SEM of data from 5-37 animals per dose.

Capsaicin aerosol is known to promote release of the
30 tachykinins SP and NKA from sensory nerves in the airways
of guinea pigs which may then act upon NK₁ and NK₂
receptors, respectively to elicit respiratory effects.
The ability of the compounds of Example 3A; and Example
20A to attenuate capsaicin-induced respiratory effects,
35 shown in Table 7a, is inferred from their ability to
reduce incidence of dyspnea, prolong the onset of the
response and reduce the number of coughs/gasps which occur
during aerosol exposure. The compound of Example 3A as

well as the compound of Example 5 also antagonize the effects of capsaicin aerosol when administered orally as shown in Table 7b. These data suggest that the compounds of Example 3A; Example 20A; and Example 5 inhibit the endogenous tachykinins released by capsaicin aerosol which produce respiratory alterations in conscious guinea pigs *in vivo*.

TABLE 7a.

Modulation of Respiratory Effects Produced by Capsaicin Aerosol in Conscious Guinea Pigs: Intravenous Administration of Putative Tachykinin Antagonists

TREATMENT	DYSPNEA INCIDENCE	DYSPNEA ONSET (sec)	MAXIMUM PRESSURE INCREASE (mmH ₂ O)	SRE NUMBER*
Vehicle	100% (60/60)	286 ± 14.3	1.09 ± 0.05	10.4 ± 0.88
Example 3A				
10 mg/kg	89% (7/8)	480 ± 80	0.83 ± 0.18	8.50 ± 1.9
Example 20A				
1 mg/kg	77.8% (7/9)	331 ± 22	1.0 ± 0.1	9.9 ± 2.7
2.5 mg/kg	100% (10/10)	426 ± 57	0.6 ± 0.1	8.3 ± 1.6
5 mg/kg	44.4% (4/9)	597 ± 186	0.8 ± 0.06	4.4 ± 1.9
10 mg/kg	55.6% (5/9)	592 ± 71	0.8 ± 0.1	3.3 ± 1.1

Values are mean and SEM of data derived from number of animals indicated in parenthesis. Putative tachykinin antagonists were administered intravenously 20 min prior to initiation of capsaicin aerosol (0.001%). *SRE number indicates the number of coughs/gasps which occurred during the 19 min capsaicin exposure period.

TABLE 7b.

5 Modulation of Respiratory Effects Produced by Capsaicin
Aerosol in Conscious Guinea Pigs: Oral Administration of
Putative Tachykinin Antagonists

TREATMENT	DYSPNEA INCIDENCE	DYSPNEA ONSET (sec)	MAXIMUM PRESSURE INCREASE (mmH ₂ O)	SRE NUMBER*
Vehicle	100% (28/28)	335 ± 32	0.8 ± 0.0	7.9 ± 1.1
Example 3A				
25 mg/kg	80% (8/10)	424 ± 120	0.7 ± 0.2	4.6 ± 1.0
50 mg/kg	70% (7/10)	434 ± 152	0.4 ± 0.1	2.8 ± 0.8
100 mg/kg	50% (5/10)	360 ± 120	0.4 ± 0.1	2.1 ± 0.5
Example 5				
25 mg/kg	66.7% (6/9)	253 ± 47	0.7 ± 0.1	4.4 ± 1.2
50 mg/kg	85.7% (6/7)	384 ± 85	0.5 ± 0.1	4.9 ± 1.9

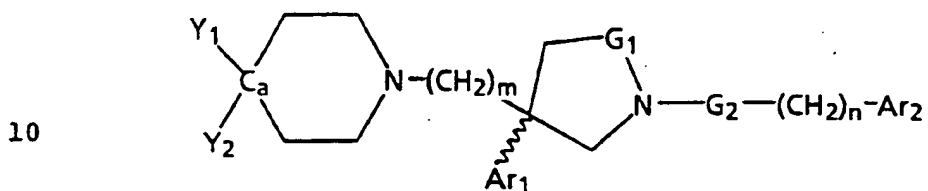
20 Values are mean and SEM of data derived from number of
animals indicated in parenthesis. Putative tachykinin
antagonists were administered by oral gavage 1 hr prior to
initiation of capsaicin aerosol (0.001%). *SRE number
indicates the number of coughs/gasps which occurred during
the 19 min capsaicin exposure period.

30

35

WHAT IS CLAIMED IS:

5 1. A compound of the formula



15 wherein

G₁ is -CH₂- or -C(O)-;

20 G₂ is -CH₂- or -C(O)-;

m is 2 or 3;

n is 0 or 1;

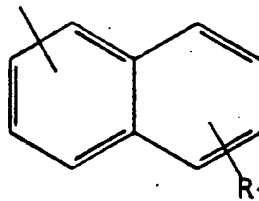
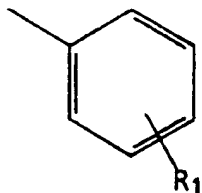
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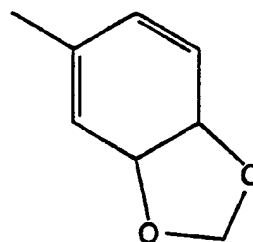
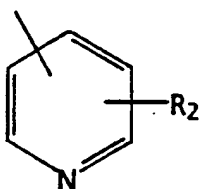
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Ar₁ is a radical chosen from the group:

5

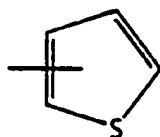


10



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wherein

25

R₁ is from 1 to 3 substituents each independently chosen from the group consisting of hydrogen, halogen, hydroxy, CF₃, C₁-C₆ alkyl, and C₁-C₆ alkoxy;

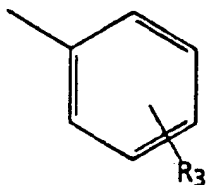
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R₂ is from 1 to 2 substituents each independently chosen from the group consisting of hydrogen, halogen, C₁-C₆ alkyl, and C₁-C₆ alkoxy;

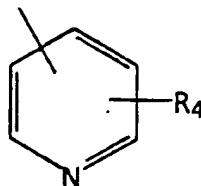
35

Ar₂ is a radical chosen from the group

5



10



wherein

15

R₃ is from 1 to 3 substituents each independently chosen from the group consisting of hydrogen, halogen, C₁-C₆ alkyl, and C₁-C₆ alkoxy;

20

R₄ is from 1 to 2 substituents each independently chosen from the group consisting of hydrogen, halogen, C₁-C₆ alkyl, and C₁-C₆ alkoxy;

Y₁ when selected individually is -C(O)NHR₅, -C(O)NR₆R₇, or -C(O)NR₈R₉

25

wherein

30

R₅ is chosen from the group consisting of hydrogen, C₁-C₆ alkyl, 3-hydroxy-2-butyryl-C₁-C₆ alkyl ester, 2-glutaryl-C₁-C₆ alkyl ester, and -CH₂CH₂N(CH₃)₂;

R₆ is C₁-C₆ alkyl;

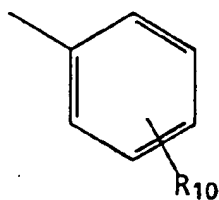
R₇ is C₁-C₆ alkyl;

35

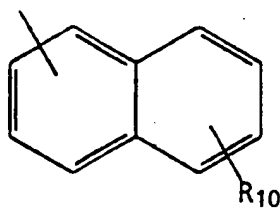
R₈ and R₉ taken together with the bonded nitrogen form a morpholine ring, piperidine ring, 4-methylpiperazine ring, or pyrrolidine ring;

Y₂ when selected individually is a radical chosen from the group

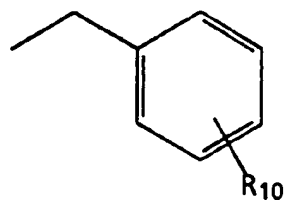
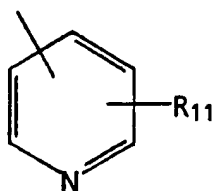
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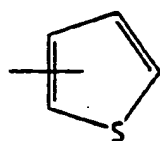
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15



20



wherein

25

R₁₀ is from 1 to 3 substituents each independently chosen from the group consisting of hydrogen, halogen, CF₃, C₁-C₆ alkyl, and C₁-C₆ alkoxy;

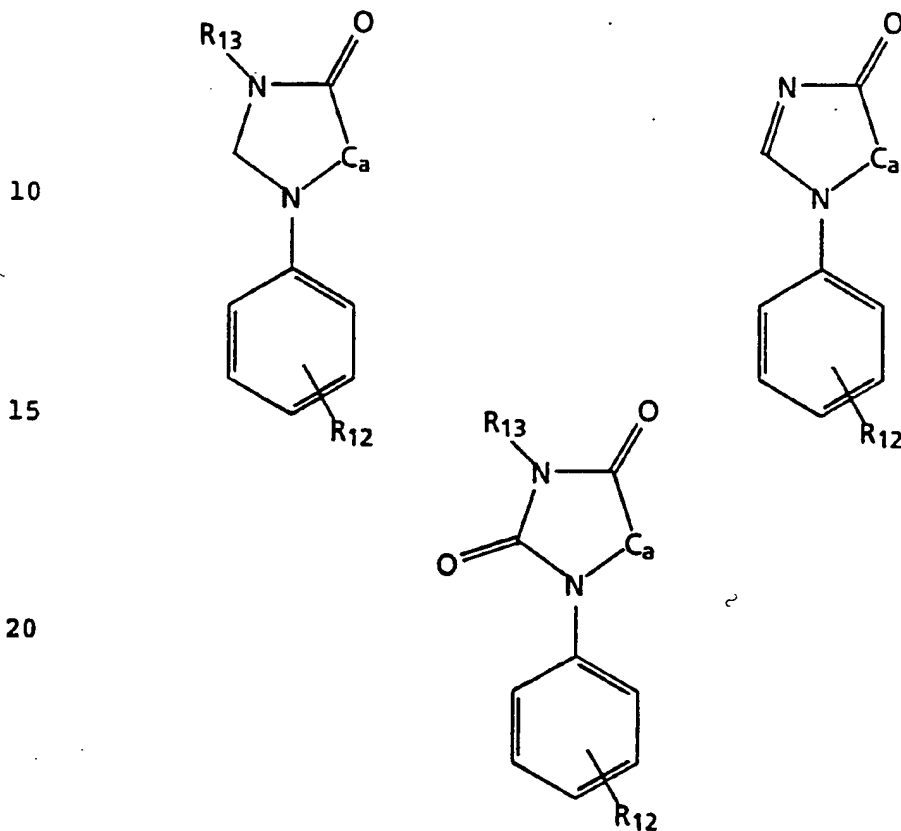
30

R₁₁ is from 1 to 2 substituents each independently chosen from the group consisting of hydrogen, halogen, C₁-C₆ alkyl, and C₁-C₆ alkoxy; or

35

Y₁ and Y₂ together with their attached carbon form a spirocyclic ring chosen from the group

5



10

15

20

wherein

the attached carbon is C_a;

25

R₁₂ is from 1 to 3 substituents each independently chosen from the group consisting of hydrogen, halogen, CF₃, C₁-C₆ alkyl, and C₁-C₆ alkoxy;

30

R₁₃ is hydrogen, C₁-C₆ alkyl, or benzyl;

or stereoisomers, or pharmaceutically acceptable salt thereof.

2. A compound of Claim 1 wherein m is 2.
3. A compound of Claim 1 wherein G₁ is -CH₂- and G₂ is
5 -C(O)-.
4. A compound of Claim 1 wherein G₁ is -C(O)- and G₂ is
-CH₂-.
- 10 5. A compound of Claim 1 wherein the compound is (+)-
or (-)-8-[2-[3-(3,4-dichloro-phenyl)-1-(2,6-dimethoxy-
benzoyl)-pyrrolidin-3-yl]-ethyl]-1-phenyl-1,3,8-triaza-
spiro[4.5]decane-4-one or a mixture thereof.
- 15 6. A compound of Claim 1 wherein the compound is (+)-
or (-)-1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-
benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-
carboxylic acid amide or a mixture thereof.
- 20 7. A compound of Claim 1 wherein the compound is (+)-
or (-)-1-[2-[3-(3,4-dichloro-phenyl)-1-(2,6-dimethoxy-
benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-
carboxylic acid amide or a mixture thereof.
- 25 8. A compound of Claim 1 wherein the compound is (+)-
or (-)-1-(2-[3-(3,4-dichloro-phenyl)-1-[2-(2-methoxy-
phenyl)-acetyl]-pyrrolidin-3-yl]-ethyl)-4-phenyl-
piperidine-4-carboxylic acid amide or a mixture thereof.
- 30 9. A compound of Claim 1 wherein the compound is (+)-
or (-)-1-[2-[3-(3,4-dichloro-phenyl)-1-(2-methoxy-benzoyl)-
pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic
acid amide or a mixture thereof.
- 35 10. A compound of Claim 1 wherein the compound is (+)-
or (-)-1-[2-[3-(3,4-dichloro-phenyl)-1-(2,4-dimethoxy-
benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-
carboxylic acid amide or a mixture thereof.

11. A compound of Claim 1 wherein the compound is (+)-
or (-)-2-[(2-[1-benzoyl-3-(3,4-dichloro-phenyl)-pyrrolidin-
3-yl]-ethyl]-4-phenyl-piperidine-4-carbonyl)-amino]-
5 pentanedioic acid dimethyl ester or a mixture thereof.

12. A compound of Claim 1 wherein the compound is (+)-
or (-)-1-[2-[1-benzyl-3-(3,4-dichloro-phenyl)-5-oxo-
pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic
10 acid amide or a mixture thereof.

13. A compound of Claim 1 wherein the compound is (+)-
or (-)-1-[2-[3-(3,4-dichloro-phenyl)-1-(benzoyl)-
pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic
15 acid amide or a mixture thereof.

14. A compound of Claim 1 wherein the compound is (+)-
or (-)-8-[2-[3-(3,4-dichloro-phenyl)-1-benzoyl-pyrrolidin-
3-yl]-ethyl]-1-phenyl-1,3,8-triaza-spiro[4.5]-decane-4-one
or a mixture thereof.

20 15. A compound of Claim 1 wherein the compound is (+)-
or (-)-2-[(1-(2-[1-benzoyl-3-(3,4-dichloro-phenyl)-
pyrrolidin-3-yl]-ethyl)-4-phenyl-piperidine-4-carboxyl)-
amino]-3-hydroxy butyric acid methyl ester or a mixture
25 thereof.

16. A compound of Claim 1 wherein the compound is (+)-
or (-)-1-[1-benzyl-3-naphthalen-2-yl-5-oxo-pyrrolidin-3-
yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide or a
30 mixture thereof.

17. A compound of Claim 1 wherein the compound is (+)-
or (-)-1-[2-(1-benzoyl-3-naphthalen-2-yl-pyrrolidin-3-yl)-
ethyl]-4-phenyl-piperidine-4-carboxylic acid amide or a
mixture thereof.

35 18. A compound of Claim 1 wherein the compound is (+)-1-
[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-

pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide.

5 19. A compound of Claim 1 wherein the compound is (-)-1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide.

10 20. A compound of Claim 1 wherein the compound is (+)- or (-)-1-[2-[3-phenyl-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide or a mixture thereof.

15 21. A compound of Claim 1 wherein the compound is (+)- or (-)-1-[2-[3-(3,4-dimethoxy-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide or a mixture thereof.

20 22. A compound of Claim 1 wherein the compound is (+)- or (-)-1-[2-[3-(3,4-dichloro-phenyl)-1-(3,5-bis-(trifluoromethyl)-pyrrolidin-3-yl)-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide or a mixture thereof.

25 23. A compound of Claim 1 wherein the compound is (+)- or (-)-1-[2-[3-(3,4-dichloro-phenyl)-1-(3,5-dimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide or a mixture thereof.

30 24. A compound of Claim 1 wherein the compound is (+)- or (-)-1-[2-[3-(3,4-dichloro-phenyl)-1-(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid (2-dimethylamino-ethyl)-amide or a mixture thereof.

35 25. A compound of Claim 1 wherein the compound is (+)- or (-)-1-[2-[3-(3,4-dichloro-phenyl)-1-(3-methoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide or a mixture thereof.

26. A pharmaceutical composition comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

5 27. A pharmaceutical composition comprising a compound of one of Claims 2-25 and a pharmaceutically acceptable carrier.

10 28. A method for treating neurogenic inflammatory diseases and conditions in a patient in need thereof comprising administering to said patient a therapeutically effective amount of a compound of Claim 1.

15 29. A method for treating asthma in a patient in need thereof comprising administering to said patient a therapeutically effective amount of a compound of Claim 1.

20 30. A method for treating pain in a patient in need thereof comprising administering to said patient a therapeutically effective amount of a compound of Claim 1.

25 31. A method for treating respiratory disease in a patient in need thereof comprising administering to said patient a therapeutically effective amount of a compound of Claim 1.

30 32. A method for treating cough in a patient in need thereof comprising administering to said patient a therapeutically effective amount of a compound of Claim 1.

AMENDED CLAIMS

[received by the international Bureau on 27 October 1994 (27.10.94);
original claims 28-30 amended; remaining claims unchanged (1 page)]

26. A pharmaceutical composition comprising a compound
5 of Claim 1 and a pharmaceutically acceptable carrier.

27. A pharmaceutical composition comprising a compound
of one of Claims 2-25 and a pharmaceutically acceptable
carrier.

10

28. A pharmaceutical composition for treating neurogenic
inflammatory diseases and conditions comprising a
therapeutically effective amount of a compound according to
Claim 1 to 25 and a pharmaceutically acceptable carrier.

15

29. A pharmaceutical composition for treating asthma
comprising a therapeutically effective amount of a compound
according to Claims 1 to 25 and a pharmaceutically
acceptable carrier.

20

30. A pharmaceutical composition for treating pain
comprising a therapeutically effective amount of a compound
according to Claims 1 to 25 and a pharmaceutically
acceptable carrier.

25

31. A pharmaceutical composition for treating
respiratory disease comprising a therapeutically effective
amount of a compound according to Claims 1 to 25 and a
pharmaceutically acceptable carrier.

30

32. A pharmaceutical composition for treating cough
comprising a therapeutically effective amount of a compound
according to one of Claims 1 to 25 and a pharmaceutically
acceptable carrier.

35

FIG. 1A

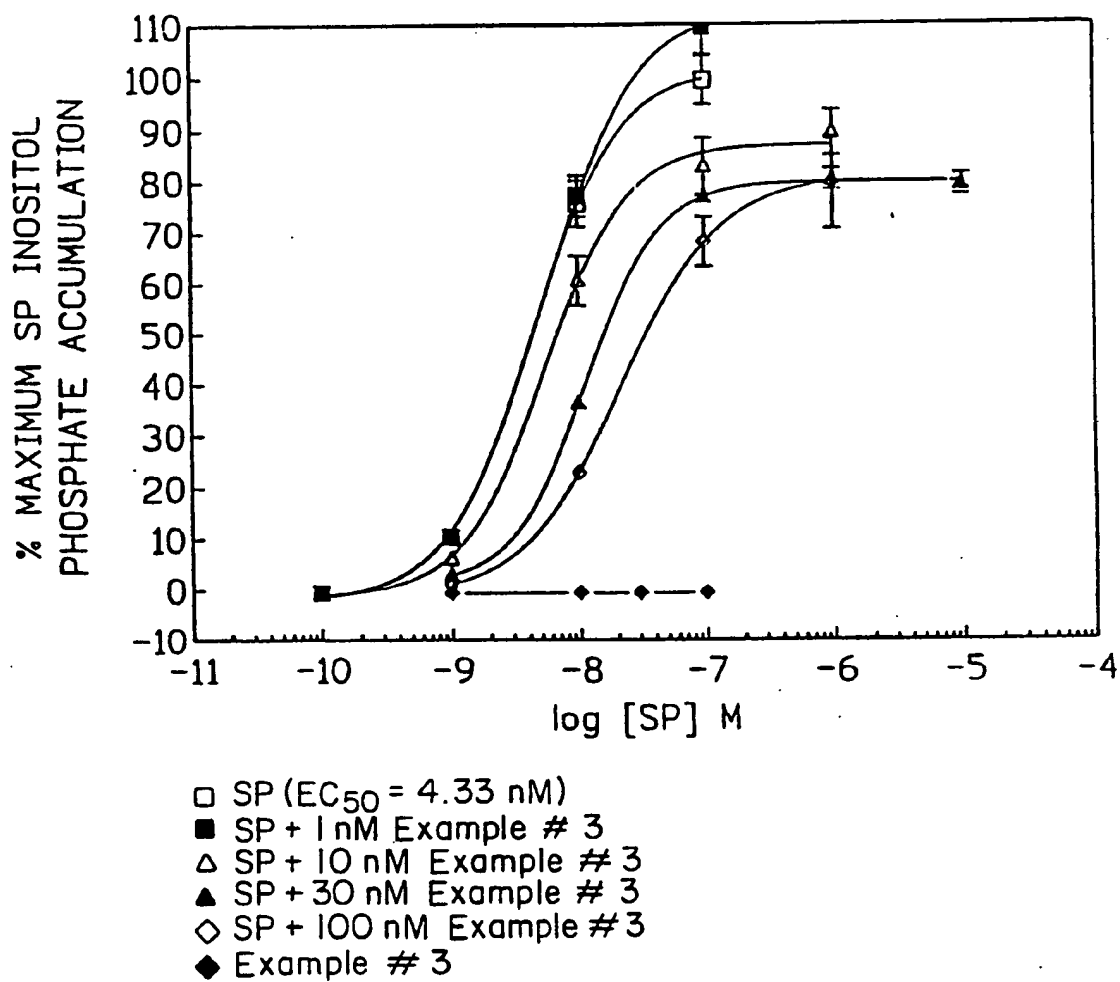
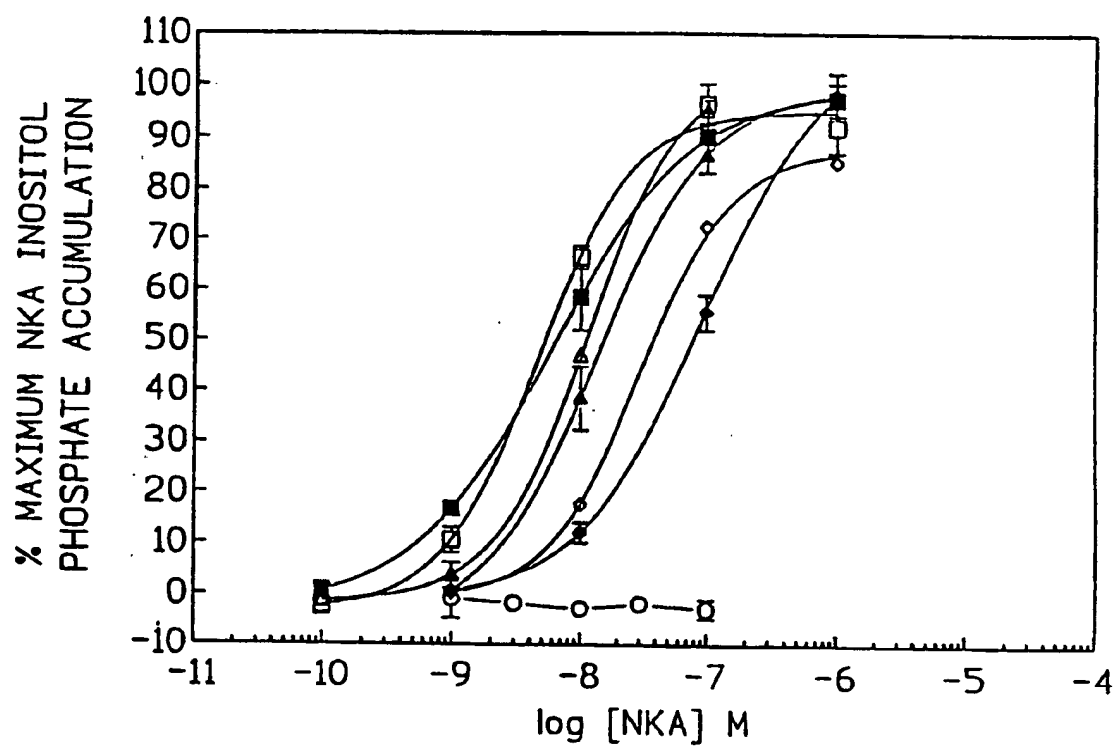
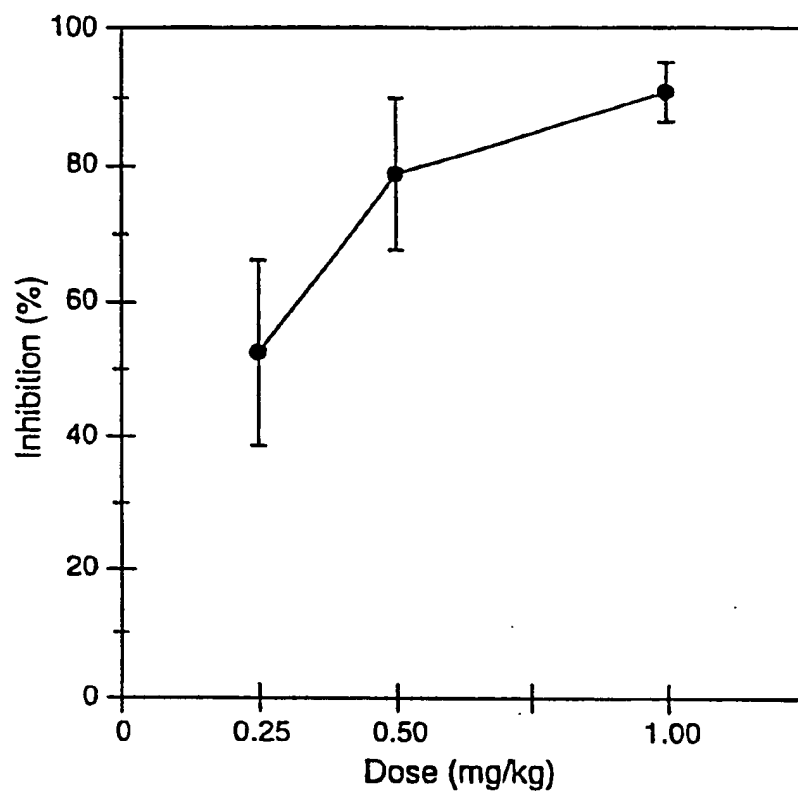


FIG. 1B



- NKA (EC₅₀ = 4.57 nM)
- NKA + 1 nM Example # 3
- △ NKA + 3 nM Example # 3
- ▲ NKA + 10 nM Example # 3
- ◇ NKA + 30 nM Example # 3
- ◆ NKA + 100 nM Example # 3
- MDL Example # 3

FIG. 2



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 94/04498

A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 C07D401/06 C07D471/10 C07D401/14 C07D405/14 C07D409/14
A61K31/445 //(C07D471/10,235:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 512 901 (ELF SANOFI) 11 November 1992 see the whole document, particularly page 22, example 4 ---	1-32
A	EP,A,0 474 561 (SANOFI) 11 March 1992 see the whole document -----	1-32

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "I" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

6 September 1994

Date of mailing of the international search report

14. 09. 94

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 94/04498**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 28-32 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds/composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/US 94/04498

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0512901	11-11-92	FR-A- 2676055	06-11-92
		AU-B- 652046	11-08-94
		AU-A- 1591692	05-11-92
		JP-A- 5186425	27-07-93

EP-A-0474561	11-03-92	FR-A- 2666335	06-03-92
		FR-A- 2678267	31-12-92
		AU-A- 8354291	12-03-92
		CA-A- 2050639	06-03-92
		JP-A- 4261155	17-09-92
		NZ-A- 239661	27-06-94
US-A- 5236921	17-08-93		
